"EVALUATION OF DRY EYE STATUS IN TYPE II DIABETICS AND ITS ASSOCIATION WITH SEVERITY OF DIABETIC RETINOPATHY"

Dissertation submitted by

DR.N.DHIVYA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY

IN

OPHTHALMOLOGY

THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY

APRIL 2017

DEPARTMENT OF OPHTHALMOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH

COIMBATORE

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled "**EVALUATION OF DRY EYE STATUS IN TYPE II DIABETICS AND ITS ASSOCIATION WITH SEVERITY OF DIABETIC RETINOPATHY**" is a Bonafide and Genuine Research work done by **DR.N.DHIVYA** in partial fulfillment of the requirement for the degree of MASTER OF SURGERY IN OPHTHALMOLOGY as per regulations of **PSG INSTITUTE OF MEDICAL SCIENCE & RESEARCH, COIMBATORE**. I have great pleasure in forwarding this to the University.

Place : Coimbatore

Date :

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled "**EVALUATION OF DRY EYE STATUS IN TYPE II DIABETICS AND ITS ASSOCIATION WITH SEVERITY OF DIABETIC RETINOPATHY**" is a Bonafide and Genuine Research work carried out by me under the guidance of **DR.K.DIVYA, M.S.,** Associate Professor, Department of Ophthalmology, PSG Institute of Medical Sciences & Research, Coimbatore in partial for the award of M.S. Degree in Ophthalmology to be held in 2017. This dissertation has not been submitted in part of full to any other University or towards any other degree before this below mentioned date.

Place : Coimbatore

Date :

Signature of the Candidate

DR.N.DHIVYA

ENDORSEMENT BY THE HEAD OF THE DEPARTMENT

This is to certify that the dissertation entitled "**EVALUATION OF DRY EYE STATUS IN TYPE II DIABETICS AND ITS ASSOCIATION WITH SEVERITY OF DIABETIC RETINOPATHY**" is a Bonafide and Genuine Research work done by **DR.N.DHIVYA** under the guidance of **DR.DIVYA.K M.S.,** Associate Professor, Department of Ophthalmology, PSG Institute of Medical Sciences & Research.

Place : Coimbatore

Date :

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Professor and Head

Department of Ophthalmology

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& Research, Coimbatore

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the dissertation entitled "**EVALUATION OF DRY EYE STATUS IN TYPE II DIABETICS AND ITS ASSOCIATION WITH SEVERITY OF DIABETIC RETINOPATHY**" is a Bonafide and Genuine Research work done by **DR.N.DHIVYA** under the guidance of **DR.DIVYA.K M.S.,** Associate Professor, Department of Ophthalmology, PSG Institute of Medical Sciences & Research.

Place : Coimbatore

Date :

DR.S.RAMALINGAM

Principal

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Institutional Human Ethics Committee

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To
Dr N Dhivya
Postgraduate
Department of Ophthalmology
Guides: Dr K Divya / Dr D Sundar
PSG IMS & R
Coimbatore

Ref: Project No.15/429

Date: December 29, 2015

Dear Dr Dhivya,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 28.12.2015 to conduct the research study entitled *"Evaluation of dry eye status in type 2 diabetes and its correlation with severity of diabetic retinopathy"* during the IHEC meeting held on 29.12.2015.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol (Version 1 dated 28.12.2015)
3. Informed consent forms (Version 1 dated 28.12.2015)
4. Data collection tool (Version 1 dated 28.12.2015)
5. Current CVs of Principal investigator, Co-investigators
6. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 29.12.2015 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr. R. Nandakumar	BA., BL	Legal Expert, Chairperson	Male	No	Yes
2	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
3	Dr Sudha Ramalingam (Alternate Member-Secretary	MD	Ethicist, Epidemiologist	Female	Yes	Yes
4	Mrs P Rama	M Pharm	Member	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

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Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
   d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
   e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
   f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr Sudha Ramalingam
Alternate Member - Secretary
Institutional Human Ethics Committee

PSG Institute of Medical Sciences & Research
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January 10, 2017

To
Dr N Dhivya
Postgraduate
Department of Ophthalmology
Guide/s: Dr K Divya / Dr D Sundar
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee PSG IMS & R, Coimbatore - 4, has reviewed your proposal on 6th January 2017 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your request to renew the approval for the study entitled:

"Evaluation of eye status in type 2 diabetes and its correlation with severity of diabetic retinopathy"

The following documents were received for review:

1. Request for renewal dated 26.12.2016
2. Status Report

After due consideration, the Committee has decided to renew the approval for the above study.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr R Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr S Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr Sudha Ramalingam	MD	Epidemiologist, Ethicist Alt. member-Secretary	Female	Yes	Yes
5	Dr D Vijaya	M Sc., Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The approval is valid for one year (29.12.2016 to 28.12.2017).

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

SECRETARY
PSG IMSR
COIMBATORE-641004
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member – Secretary
Institutional Human Ethics Committee

ACKNOWLEDGEMENT

This dissertation work has been an unforgettable journey during the course of my studies and will remain a time of my life which I would cherish forever.

My Guide **Dr.Divya.K** has been an unending source of inspiration and encouragement to me, not only in my dissertation work, but in all aspects of studies and beyond. Her reassuring presence and calm composure during difficult times have guided me as much as her unfailing wisdom and knowledge has. Without her support, completion of this thesis could have remained a distant dream.

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I also thank to my friends and colleagues who have helped and co-operated in all their means in completion of this study which would had not been possible for me to deal with alone.

A special thanks to my spouse **Dr.Karthik.R** for his motivation and constant support in my thesis work and my career. I would like to thank my parents and my family members for their support during the tough times. Lastly I would like to dedicate my thesis to my daughter Mitra.K who has been the driving force throughout my post graduation.

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The Prevalence of Dry Eye among the population of Chennai, India.docx (D20213193)
Clinical changes among contact lens wearers with dry eye symptoms by using tear lubricant.docx (D29447576)

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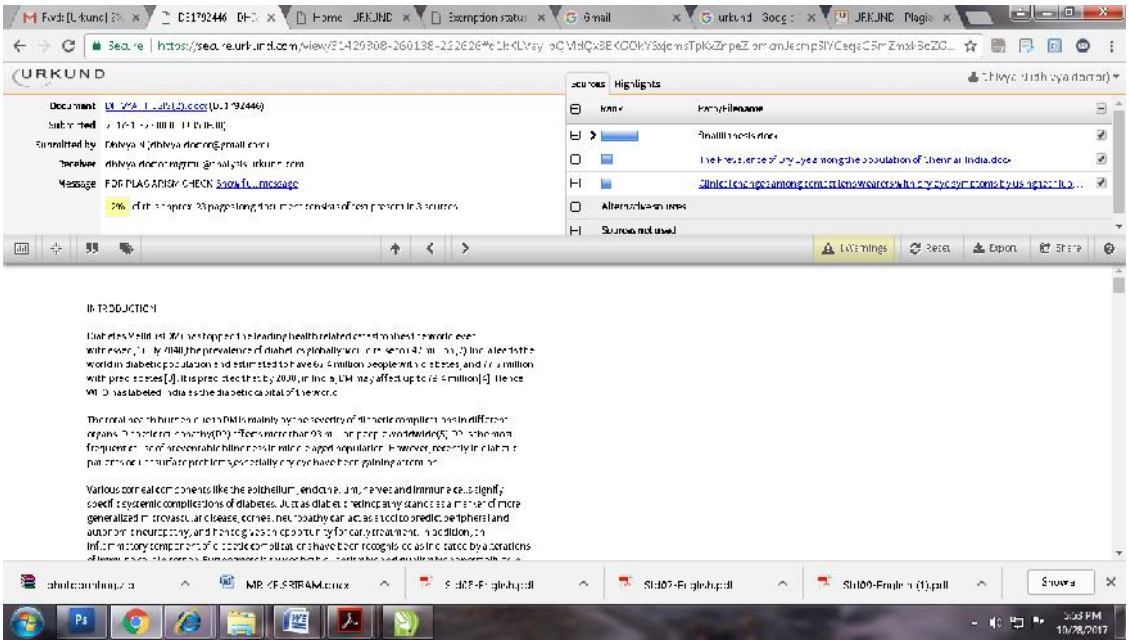
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INTRODUCTION

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INTRODUCTION

Diabetes Mellitus(DM) has topped the leading health related catastrophes the world ever witnessed(1). By 2040,the prevalence of diabetics globally would raise to 642 million(2).India leads the world in diabetic population and estimated to have 62.4 million people with diabetes, and 77.2 million with prediabetes (3). It is predicted that by 2030, in India, DM may affect up to 79.4 million(4). Hence WHO has labeled India as the diabetic capital of the world.

The total health burden due to DM is mainly by the severity of diabetic complications in different organs. Diabetic retinopathy(DR) affects more than 93 million people worldwide(5).DR is the most frequent cause of preventable blindness in middle aged population. However, recently in diabetic patients ocular surface problems,especially dry eye have been gaining attention.

Various corneal components like the epithelium, endothelium, nerves and immune cells signify specific systemic complications of diabetes. Just as diabetic retinopathy stands as a marker of more generalized microvascular disease, corneal neuropathy can act as a tool to predict peripheral and autonomic neuropathy, and hence gives an opportunity for early treatment. In addition, an inflammatory component

of diabetic complications have been recognisied as indicated by alterations of immune cells in cornea. Furthermore it causes both quantitative and qualitative abnormalities in tear secretion, decreased corneal sensitivity and poor adhesion of regenerating epithelial cells.

All these imply an widespread disease of the ocular surface due to diabetes including common diseses like dry eye, recurrent corneal erosions to severe complications like corneal ulcerations, superficial punctate keratopathy and persistent epithelial defects. Close monitoring of diabetic patients as well as glycemic control is important for the prevention of dry eye syndrome.Early diagnosis of dry eye syndrome in diabetic patients is important for improving the ocular surface and quality of vision(6).

We aimed to study the changes of tear film and ocular surface in diabetics by assessing, the symptoms of dry eye using OSDI questionnaire, tear secretion using Schirmer's test, tear film break‑up time (TBUT),and the surface with the staining score by oxford scheme, there by detecting the dry eye status in diabetics and also by comparing the results with those of healthy controls.

REVIEW OF LITERATURE

DRY EYE SYNDROME AND OCULAR SURFACE DISEASE:

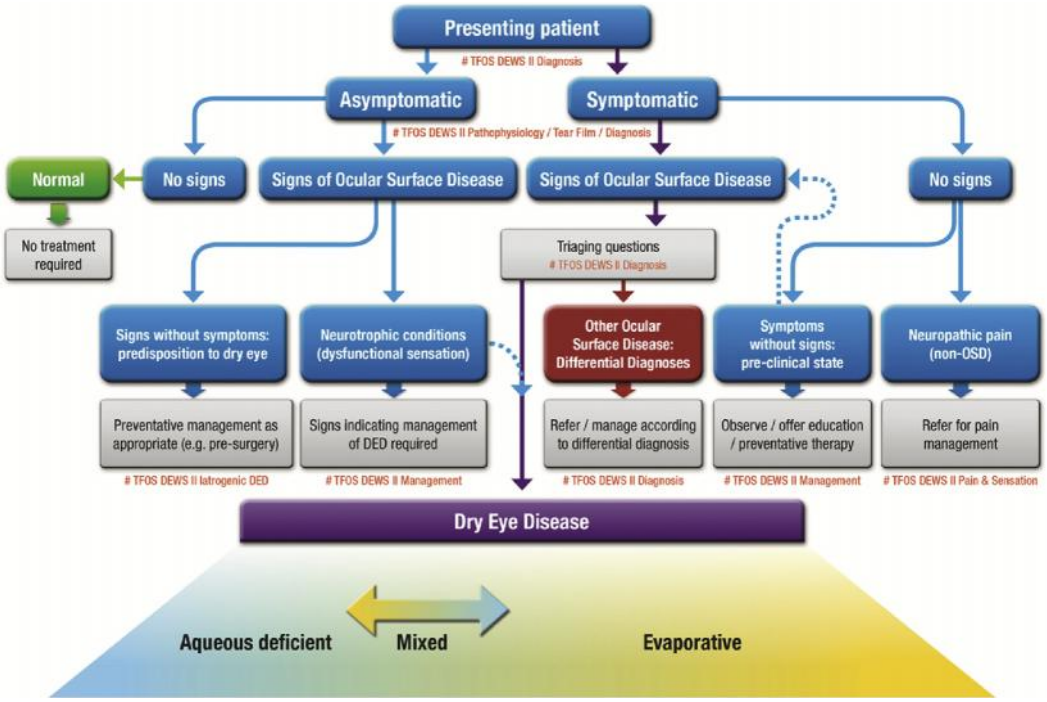
The ocular surface is one of the most complex tissues of the body. Stability of ocular surface enables protection and also forms an effective refractive media for good quality of vision. Hence any condition which affects the stability and functioning of tearfilm leads to onset of ocular surface disease and dry eye syndrome.

DRY EYE-DEFINITION:

According to Dry Eye Workshop (DEWS) II 2017, the definition is revised as “Dry eye is a multifactorial disease of ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”(7)

CLASSIFICATION:

A new patient centric approach to classification have been postulated in the DEWS II report, which helps in more understanding of dry eye.



Accordingly, it is divided depending on either the patient is symptomatic or asymptomatic and then divided further into strata based on the presenting symptoms, with corresponding clinical signs, into four branches: asymptomatic with and without signs, also symptomatic patients with and without signs.

Asymptomatic individuals without signs are normal, while asymptomatic patients with signs are grouped as at risk of developing symptoms iatrogenically (ie either following ocular procedures or other therapeutic interventions). Symptomatic individuals with signs are further divided into those with dry eye and those with other ocular surface diseases (e.g., allergy, ocular cicatricial pemphigoid). Symptomatic

individuals with no signs may have neuropathic pain or have a pre-clinical dry eye.

Again the etiological classification proposed by DEWS II in 2017 consists of three types,

1) Aqueous deficient dry eye (ADDE)
2) Evaporative dry eye (EDE)
3) Mixed dry eye

This new classification includes a mixed dry eye group where both aqueous deficient and evaporative dry eye can occur together and thus require management of both in one patient.(7)

EPIDEMIOLOGY:

Age, sex and geographical location play key factors for prevalence of dry eye disease(8). Increase in age, females have more prevalence of dry eye and likely higher prevalence in Asians than in Caucasian population(9,10). Other main factors that affect prevalence of dry eye disease are diabetes and other systemic diseases, environmental factors, contact lens wear, refractive surgery and computer system use(11).

While there appear a female preponderance for dry eye disease, Meibomian gland dysfunction (MGD) which act as a important causative

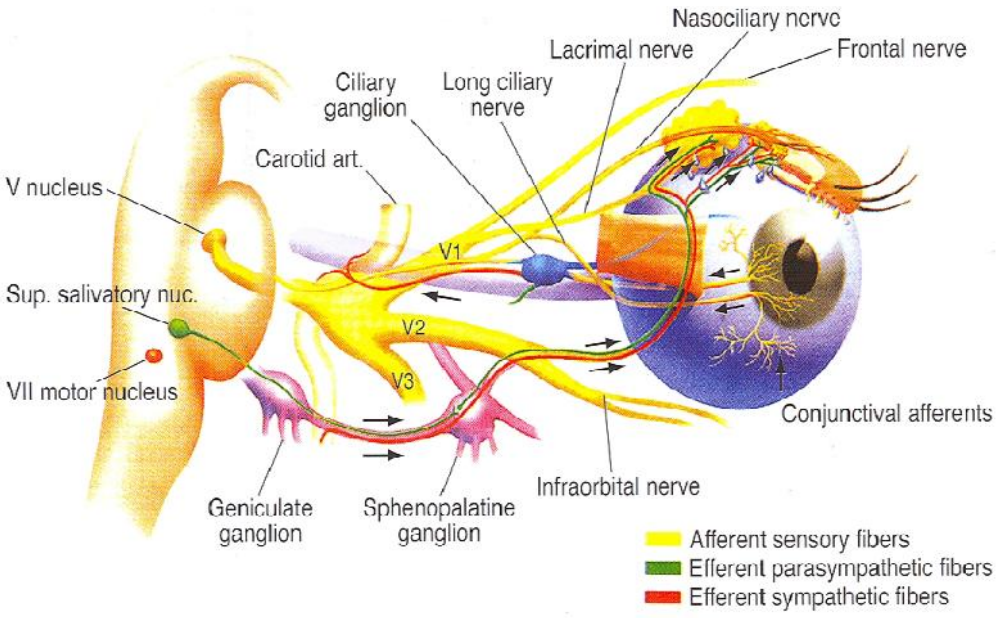
for dry eye disease show no female predilection and males have a slightly higher prevalence in most age categories.

Most studies which are sign-based showed increase prevalence with age; while, symptomatic disease was higher in younger age groups(search south east asia studies-12)

PATHOGENESIS:

The lacrimal functional unit (LFU) consists of the secretory glands mainly lacrimal, lids and the ocular surface comprising cornea, conjunctiva and meibomian glands . These are linked by a neural network, and helps in responding to external stimuli to maintain stability of tear film and ocular surface, which is essential for a clear vision.(13)

THE LACRIMAL FUNCTIONAL UNIT



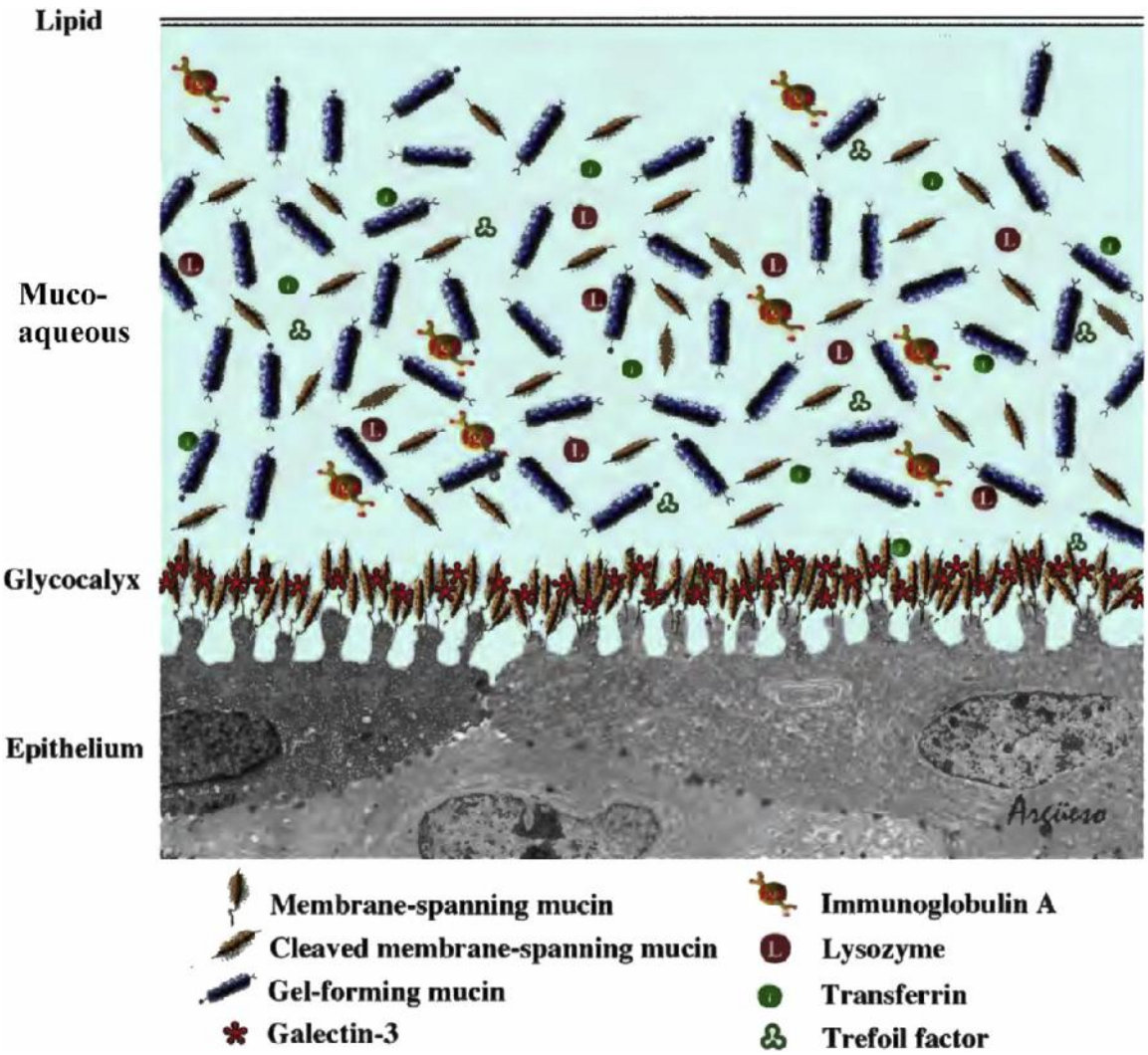
The LFU regulates the major components of the tear film and responds to environmental, endocrinologic, and cortical influences. Its overall functions are

- To maintain integrity of tearfilm thus helps in lubricating, also has antimicrobial, and nutritional roles
- Ocular surface health thereby maintaining corneal transparency and surface stem cell population
- Proving a good quality of image being projected onto the retina

Tear film:

According to the TFOS DEWS II committee report, the tear film is a single dynamic functional unit with different compartments. It consists of a lipid layer covering a complex integrated mixture of aqueous, mucins and proteins, all of which work together to maintain tear film and ocular surface homeostasis.(14)

THE TEAR FILM STRUCTURE



The muco-aqueous layer forms bulk (2-6µm) of the tearfilm. It overlies the hydrophobic apical epithelial cells and its carbohydrate-rich glycocalyx. This layer contains almost four major mucins, and over 1500 different proteins and peptides. Mucin, mainly secreted by the goblet cells of conjunctiva and small amount from the surface epithelial cells provides a smooth, hydrophilic surface permitting even distribution of the aqueous layer.(15,16)There are numerous mucins found in tears, the major soluble

mucin being MUC5AC and the transmembrane mucins being MUC1, MUC4 and MUC16.

Mucins help to stabilize and even spread of tears by binding, through their high levels of glycosylation, to water. A reduced MUC5AC expression and alteration in glycosylation of mucins is a consistent finding seen in dry eye among most studies.(14)

The aqueous solution is secreted by the lacrimal gland and the accessory glands of Krause and Wolfring. It contains 98% of water with ions of inorganic salts, glucose, urea and various biopolymers such as enzymes, proteins and glycoproteins dissolved in it. Lysozyme , lactoferrin, tear specific prealbumin and secretory immunoglobulin-A are the main constituents of protein fraction. It provides atmospheric oxygen to the epithelium, washes the debris and noxious irritants and also has antibacterial properties.

Changes in tear proteins levels and aminoacids from that of normal tears have been reported in DED subjects, but these changes are yet to be validated to aid diagnosis. If proven these can be used as possible biomarkers of the disease.

The lipid layer is thin (0.1µ thick) and secreted by the meibomian glands. It contains chiefly sterol esters and wax monoesters (16,17). The

lipid layer serves to stabilize the tear film by reducing the surface tension and retarding evaporation.

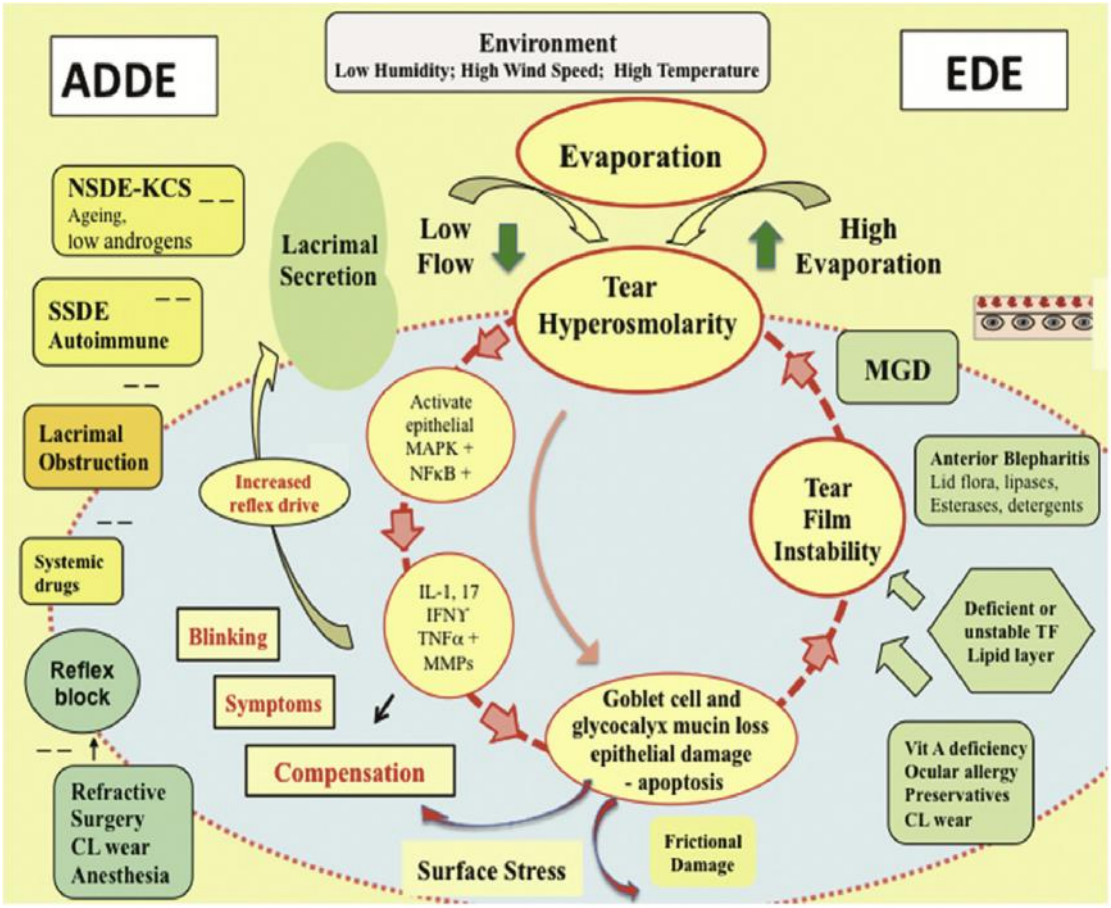
The tear film maintains a smooth surface for optical clarity, lubricates to facilitate eyelid blink, and offers protection against ocular infection(19). Average tear flow is about 1.2 μm/minute(20). Blinking serves to periodically distribute tears evenly over the ocular surface and encourages both secretion and mechanical drainage of tears through the lacrimal drainage system.

Corneal sensory neurons are broken down into three categories: polymodal nociceptors, specific mechano-nociceptors and cold thermoreceptor neurons. While polymodal nociceptors respond to chemical, mechanical and thermal stimuli and become sensitized by inflammation, mechano-nociceptors only respond to mechanical forces. The most important neurons in the pathology of dry eye, researchers suspect, are cold thermoreceptors, which discharge continuously with normal eye surface temperature and increase or decrease the fi ring frequency based on cooling or warming, respectively. These neurons also seem to be sensitive to changes in osmolarity, leading the authors to suggest that “cold-sensitive fibers contribute to the reflex control of basal tear production and blinking.

PATHOPHYSIOLOGY:

DED is initiated by damaging desiccation of ocular surface and perpetuated by a vicious circle of ocular surface inflammation. The main mechanism of DED is tear hyperosmolarity which is the hallmark of the disease. It damages the ocular surface both directly causing pain and also by inducing inflammatory signals.

THE VICIOUS CIRCLE OF DRY EYE DISEASE



Two main forms of dry eye include,

i) Evaporative dry eye (EDE)-here, the tear hyperosmolarity results from excessive evaporation from the tearfilm whereas the lacrimal function is normal.

ii) Aqueous-deficient dry eye (ADDE)-here hyperosmolarity occurs due to a reduced lacrimal secretion with normal rate of tear evaporation(14)

Since tear osmolarity can raise as a result of tear evaporation in both ADDE and EDE, it signifies all forms of DED are evaporative. EDE is thus considered to be a hyper-evaporative state. From here, the vicious circle seizes, leading to continous ocular surface damage, exacerbating signs and symptoms and often changes the condition into a hybrid form of dry eye.

In DED, hyperosmolarity sets up a cascade of signaling events in surface epithelial cells that leads to the release of inflammatory mediators and proteases. These mediators, along with the hyperosmolarity itself, cause goblet and epithelial cell loss and damage to the epithelial glycocalyx, epithelial cell death, MMP production and also amplifies the process of mitosis, thereby the release of extracellular DNA, which

activates a multicomponent inflammatory response of the ocular surface and disturbance in mucin expression.(10)

This final results in the characteristic punctuate epitheliopathy of DED and tear film instability, leading to early tear film break-up which further exacerbates and amplifies hyperosmolarity and completes the vicious circle of events. Ultimately, this causes self-perpetuation of the ocular surface damage.

The major causes of tear hyperosmolarity are decreased aqueous tear flow due to failure of the lacrimal secretion and /or excessive evaporation of the tear film. Environmental factors like low humidity, high air flow and high temperature aids to increase evaporative loss, which may also be caused clinically, by meibomian gland dysfunction (MGD), which leads to an unstable tear film lipid layer.

Tear film instability can also be caused by various other factors like xerophthalmia, ocular allergy, contact lens wear, systemic medications causing dry eyes, topical preservative use. In blepharitis, the increase in the normal eyelid commensals leads to alteration in the quality of eyelid oil due to increased release of esterases and lipases than usual.

Reduction in aqueous tear flow is mainly due to impaired delivery of lacrimal secretion into the conjunctival sac which can be physiologic due

to aging or drug induced, by certain antihypertensive agents, antihistamines, and antimuscarinic agents. The most common cause of lacrimal damage is autoimmune disorder such as Sjogren syndrome and also in non-Sjogren syndrome dry eye (NSSDE).Inflammation causes both destruction of the lacrimal gland and a neurosecretory block which could be reversible. It is due to the circulating antibodies to the M3 receptor. Low androgen levels also aids inflammation.

Other factors for a reduced tear flow may be an obstructive cicatricial conjunctival scarring or chronic ocular surface damage leading to a reduction in corneal sensitivity and reflex tear secretion due to loss of sensory reflex drive to the lacrimal gland. Various etiologies such as refractive surgeries, longterm abuse of topical anaesthetics and contact lens wear, act in part, by blocking the reflex secretion to cause dry eye.

In the initial stages of DED, the tear hyperosmolarity and epithelial injury stimulates corneal nerve endings, leading to irritation, increased blink rate and a compensatory, increase in the reflex tear secretion. Over time, damage to the ocular surface leads to reduced corneal sensation and impairment of reflex tear secretion.(21) In advanced cases of dry eye, chronic damage to the conjunctiva results in metaplasia and keratinization.

CAUSES OF DRY EYE:

AQUEOUS DEFICIENT		
Sjogren's syndrome	Primary Sjogren's syndrome	KCS with xerostomia
	Secondary Sjogren's syndrome	KCS with xerostomia assc. with connective tissue diseases such as RA, SLE, Systemic sclerosis, GVHD
Lacrimal gland deficiencies	Primary	Age-related dry eye Congenital alacrima Familial dysautonomia
	Secondary	Lacrimal gland infiltration -Sarcoidosis -Lymphoma -AIDS -GVHD -Lacrimal gland ablation -Lacrimal gland Denervation
Lacrimal gland duct obstruction		Trachoma OcMMP Erythema multiforme Chemical and thermal burns

Reflex hyposecretion		Reflex sensory block Contact lens wear Diabetes Neurotrophic keratitis Reflex motor block VII nerve damage Multiple neuromatosis
Systemic drugs		
EVAPORATIVE		
Intrinsic(direct effect on evaporation)		Meibomian oil deficiency Lid aperture problems Low blink rate Drugs
Extrinsic (indirect effect via changes to ocular surface)		Vitamin A deficiency Topical drugs/preservatives Ocular surface diseases

OCULAR MANIFESTATIONS:

Symptoms:

Typical complaints include burning sensation, itching, foreign body sensation, redness, stinging, dryness, photophobia and ocular fatigue.

Patients with aqueous tear deficiency usualy describe a diurnal pattern with increase of symptoms over the day and difficulty in specific environmental conditions such as low humidity areas like working in airline cabins, change in climate, and the use of VDU terminals.(22,23) Contrastly, increased night-time exposure, floppy eyelid syndrome, and inflammatory conditions mostly present with more discomfort upon awakening.

MGD causes intermittent visual blurring and usualy complain gritty or sandy sensation. DED in diabetes and other corneal neuropathies are asymptomatic or may have little discomfort and hence are at high risk for keratolysis.

Signs:

Common signs of DED include conjunctival injection, photophobia, decrease in tear meniscus height, increased tear debris, and

dull cornea with loss of sheen and commonly seen in the exposed interpalpebral fissure. Paradoxical epiphora in DES is usually a result of reflex tearing. Increased risk for external infections occurs secondary to decreased tear turnover and damage to the surface epithelium. Instability of the surface epithelium and disordered mucin production may cause painful and recurrent filamentary keratitis.

Patients with SSTD have severe symptoms and more serious signs than do NSTD patients. SSTD can present with peripheral or paracentral sterile corneal ulcers and can be complicated with thinning and perforation. Acute enlargement of the lacrimal gland may be seen in SSTD. It should be differentiated from benign lymphoepithelial lesion (Mikulicz's disease).(24)

DIAGNOSTIC METHODOLOGY:

The diagnostic methodology includes tests to

i) Quantify patient symptoms,

ii) Visual disturbance,

iii) Tear film stability,

iv) To measure for osmolarity,

v) To quantify tear volume,

vi) Assess ocular surface damage,

vii) Inflammation of the ocular surface and

viii) Eyelid signs (such as MGD).

Tests to quantify patient symptoms and visual disturbance:

Questionnaire's

Symptoms are recorded through the use of various questionnaire instruments that are usualy self-administered by the patient or research subject. This helps with a diagnostic score criteria to screen patients and the need for further testing. It is also helpful to enhance standardization as a tool in clinical research. The Ocular Surface Disease Index (OSDI) is the most widely used questionnaire in clinical trials due to its strong establishment in the field or the 5-Item Dry Eye Questionnaire (DEQ-5) due to its short length and discriminative ability.(25,26)

Ocular Surface Disease Index (OSDI) Questionnaire

It is a disease specific questionnaire use to quantify the frequency of symptoms, various environmental triggers and the impact of dry eye on vision related quality of life The OSDI includes 12 questions divided in 3 subscales: i)symptoms associated with visual disturbance(blurred vision, or poor vision) or ii) visual function (problems in reading, watching

Television, working on a computer, or driving at night) and iii)environmental triggers.A study by Li M, Gong et al, showed that the DED group with 87 patients had worse OSDI total score and subscale scores for vision-related function, compared to a other group with 71 patients without DED.(27)

Dry Eye Questionnaire (DEQ-5)

The DEQ has 4 questions related to visual disturbance, including the frequency of visual changes, wether diurnal variation in visual disturbance and the botherance to respondent by these variations.(28) In a study using the DEQ, reported 10% of patients with non-Sjogren syndrome DED and 30% of patients with Sjogren syndrome complained of impaired vision while others reported that between 42% and 80% of patients with primary Sjogren syndrome experienced “disturbances in daily vision”.

Various other questionnaire available are Impact of Dry Eye on Everyday Living (IDEEL), National Eye Institute's Visual Function Questionnaire (NEI VFQ-25), Dry Eye-Related Quality-of-Life Score (DEQS), Computer-Vision Symptom Scale (CVSS17), McMonnies' Questionnaire(MQ), Ocular Comfort Index (OCI and OCI-C), Symptom Assessment in Dry Eye (SANDE).

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned? . . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

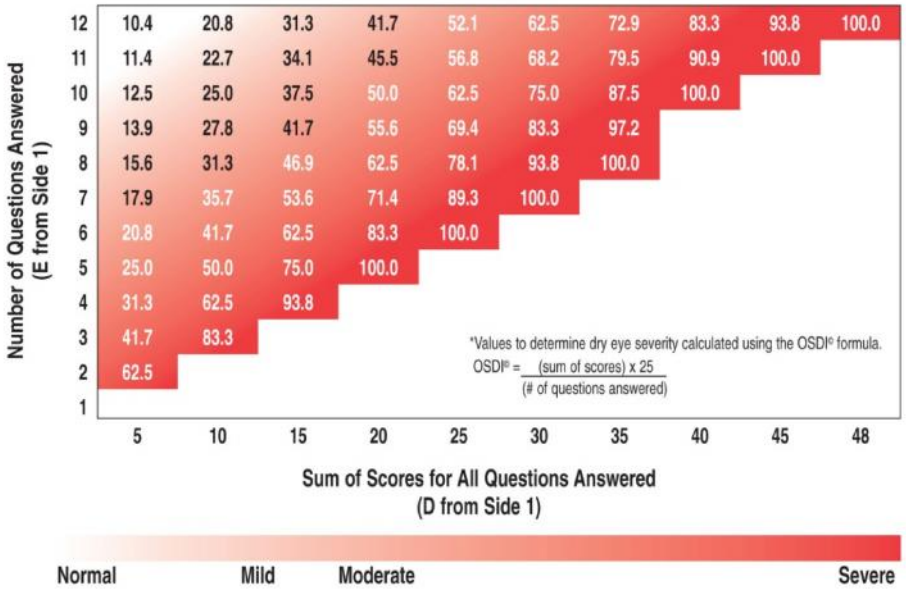
Please turn over the questionnaire to calculate the patient's final OSDI© score.

Evaluating the OSDI© Score[1]

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI© is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



Patient's Name: _____ Date: _____

How long has the patient experienced dry eye disease? _____

Eye Care Professional's Comments: _____

1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Function tests:

Standard distance and near visual acuity testing, using Early Treatment Diabetic Retinopathy Study (ETDRS) and Lighthouse near vision charts, showed significant decrease in visual acuity in symptomatic and asymptomatic OSD patients. Functional visual acuity (FVA) tests using Landolt optotypes which tests functional vision for daily activities is reduced in DED patients more than in controls, due to irregular ocular surface and induced higher order aberrations.(30,31,32)

Tests for tear film stability:

1. Fluorescein Tear break-up time (TBUT)
2. Non-invasive tear breakup time (NIBUT)
3. Tear Interferometry
4. Thermography
5. Tear evaporation rate

1. Fluorescein Tear break-up time (TBUT)

Tear break-up time is measured as the time interval between the last blink and the appearance of the first randomly distributed black spot on the pre corneal tear film seen using the cobalt blue filter on the slit

lamp microscope. The test is referred to as the fluorescein breakup time (FBUT) when Sodium fluorescein dye 1mg impregnated strips (commonly used) is instilled to enhance visibility of the tear film The reference value for diagnosis of DED ranges from a cut-off time of less than 10 seconds. (33) The European Community Study Group on diagnostic criteria for Sjogren's Syndrome reported the sensitivity and specificity of the test to be 72.2% and 61.6%, respectively, in patients with Sjogren Syndrome (34); however, mild and moderate DED patients have varied range of FBUT values and the diagnostic value is less certain.(35)

2. Non-invasive tear breakup time (NIBUT)

These techniques involve the observation of the reflection of regular pattern from the tear film and measures the time for it to break-up following the last blink.ker of definitive dry eye. A value of more than 10 seconds is normal while less than 5 seconds is marker of definite dry eye.(36) Xeroscope, Placido-based computerisied videokeratoscopy is used to determine NIBUT. The tear breakup pattern for tear lipid deficiency tends to be linear on the inferior and central cornea compared with random circular breakup pattern over areas of punctuate epitheliopathy for aqueous tear deficiency. Automated assessment of tear film stability is done with specific software on instruments such as the

Keratograph (Oculus, Wetzlar, Germany), which detects and maps locations of tear breakup over time.(37,38). The sensitivity and specificity ranges from values of 82-84% sensitivity and 76-94% specificity according to the specific technique used.(38-40)

3. Tearfilm interferometry

Interferometry, an non invasive technique used to assess the stability of the tear film measures the thickness of precorneal tear film, using wavelength –dependent fringes; the optical path difference from the reflection at the surface of the tear film and at the interface of the tear film and cornea results in an interference wave, which is calculated to be the precorneal tear film thickness(41). Normal precorneal tear thickness varies from 2.7 to 11.0 µm. In this method, the lipid layer of the tear film can also be evaluated. In dry eye due to lipid deficiency,lipid spreads slowly with vertical streaking patterns compared to rapid spreading in horizontal pattern in normal subjects. (42,43)

4. Thermography

Infrared thermography is a non-invasive method which measures the temperature of the ocular surface and gives an objective, quantitative output. (44) It is based on the principle that evaporation of the tear film leads to cooling of the ocular surface(45), and therefore measuring the

absolute temperature and the spatial and temporal changes in temperature during the inter-blink period, can be used as an index of tear film stability. Literature indicates that the cooling rate of the ocular surface is faster in individuals with DED than in normal eyes, which is responsible for the greater of evaporation of tearfilm.(46-48). Recently, thermography is used to differentiating various aetiologies, ADDE (with the lowest temperatures and higher cooling rates) and EDE (lower rates)(49).

5. Tear evaporation rate

The tear evaporation rate is used as an important indicator of tear film stability.(50) It is measured using different techniques such as a vapour pressure gradient(51,52) and resistance hygrometry - which measures the velocity of relative humidity increase within a goggle cup placed over the eye.(53,54) Higher the evaporation rates between blinks poorer is the tear film stability(55),and dry eye symptoms (54,56,57).It is difficult to use it as a diagnostic tool since the evaporation rate is dependent on humidity, ambient temperature, and time of day at which it is measured and it can also be affected by evaporation from the skin surrounding the eye. There has been two-fold increase in evaporation rate reported in patients with KCS(54).

Tests to measure tear osmolarity:

Tear osmolarity of all clinical DED tests, is said to have the highest correlation to disease severity (58). It is also the single best objective marker useful in diagnosing and classifying Dry eye disease (59,60). The osmolarity is measured using TearLab test (TearLab Corp, San Diego, CA, USA) with 50 µl tear sample with minimal disturbance to the tear film. It is classified as normal (302.2 ± 8.3 mOsm/L), mild-to moderate(315.0 ± 11.4 mOsm/L) and severe (336.4 ± 22.3 mOsm/L).(58)

Tests to measure tear volume:

1. **Schirmer test**
2. **Tear meniscometry**
3. **Phenol thread test**

1. Schirmer test

The volume is the measured based on wetting of the whatmann filter paper 41strip (5 x 35 mm) by hooking the folded notch at the junction of middle one third and the temporal one third of the lower lid margin for a period of 5 minutes. This test can be performed with (schirmer II) and without (schirmer I) anaesthesia. Schirmer I is a well standardized test which accounts for the measure of both basal and reflex

secretion of tears. The test done with the patient's eye closed minimizes the variability of results (61). Less than 10 mm of wetting without anaesthesia or less than 6 mm of wetting with anaesthesia after 5 minutes is considered abnormal.(62,63).

2. Tear meniscometry

The majority of tear fluid is present within the menisci (64) which is formed by the tears lying at the junctions of the margins of both the upper and lower eyelids and of the bulbar conjunctiva and these act as reservoir to the precorneal tear film(65). Recently , the most appropriate method to study the tear volume is quantitative assessment of the tear menisci. The tear menisci are assessed for its height(TMH), cross-sectional area(TMA) and the meniscus curvature(TMR). The influenctial factors include time after a blink, measurement site along the lid margin, time of day measured, temperature, humidity, speed of air at the locus, and illumination (66,67). Various techniques used to assess the tear menisci are conventional video-meniscometry, Slit-lamp mounted digital meniscometer, Portable digital meniscometry and optical coherence tomography (OCT) meniscometry (68,69). T OCT meniscometry (Visante anterior segment OCT; Carl Zeiss Meditec, international, Dublin, CA, USA), is advantageous in that it is non-invasive and rapid

image acquisition is rapid, but analysis of the image may be complex, time consuming and operator-dependent (62).

3. Phenol red thread test (PRT)

This test consists of placing a thin cotton thread soaked with phenol red, a pH sensitive dye within the outer one-third of the eyelid margin for 15 seconds. When moistened by tears the yellow thread turns red due to slight alkaline pH of the tears. In practice, the cut-off value of 20 mm has been accepted to differentiate aqueous deficient DED with others.(62)

Tests to assess the ocular surface integrity:

1. Ocular surface staining
2. Impression cytology
3. In vivo confocal imaging
4. Ocular surface sensitivity

1. Ocular surface staining

Staining helps to assess the integrity of the superficial cell layer of the ocular surface. The various stains used are: sodium fluorescein, rose bengal and lissamine green. Fluorescein sodium is the most common

stain used in clinical practice. It stains the disrupted surface(disruption in cell- cell tight junctions or defective glycocalyx) and not the normal cornea due to poor penetrability of stain through the lipid layer. It is seen better with blue-free filter.(70,71)

Rose Bengal-a derivative of fluorescein, stains ocular surface epithelial cells that are lacking membrane associated mucin or glycocalyx, as well as dead or degenerated cells. On instillation, it produces stinging sensation and induces reflex tearing. It has also been shown to be toxic to human corneal epithelial cell (72,73).

Lissamine green-a synthetic organic acid dye, stains epithelial cells only when the cell membrane is damaged, irrespective of the presence of mucin. It is well tolerated and less toxic than rose Bengal (74). A red filter (567-634 nm) is used to enhance contrast against the sclera thereby, staining visibility.(75)

Sequential staining increases the likelihood of ocular surface damage. Various grading systems are present to assess the severity of ocular surface stainig which includes the van Bijsterveld system, the Oxford Scheme, the National Eye Institute/Industry(NEI) Workshop guidelines, the area-density combination index, the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) schema, and the

Sjogren's International Collaborative Clinical Alliance ocular staining score (76-81).

Van Bijsterveld grading

It uses rose bengal staining of the conjunctiva and cornea. Staining is evaluated on the scale of 0-3 in 3 areas-the nasal and temporal triangular areas of conjunctiva and the cornea with a maximum score of 9. A score greater than 3 is considered abnormal.

The NEI Workshop grading

It uses fluorescein and rose-bengal for conjunctiva. A score of >3 out of 15 and >3 out of 18 is considered abnormal for cornea and conjunctiva respectively.

Oxford scheme

The cornea and conjunctiva is graded together using fluorescein and rose bengal or lissamine green stain. The epithelial damage is graded using a chart with series of panels labeled A-E in order of severity (absent,minimal,mild,moderate,severe).

The severity using oxford scheme is graded as

Grade 0-1: Normal

Grade 2: Mild

Grade 3: Moderate

Grade >4: Severe

2. Impression cytology

Cells from the superficial 2-3 layers of the epithelium are removed from the area of interest by applying cellulose acetate filters or biopore membranes and then air dried and stained with periodic acid – sciff and hematoxylin. These subsequently analyzed by subjecting to various methods like microscopy, immunocytochemistry and molecular testing. Squamous metaplasia and goblet cell density of the conjunctiva are assessed using various cytological criteria (Nelson-widely used, Tseng, and Blade) for the diagnosis and monitoring of DED.(82-89)

3. In vivo confocal microscopy (IVCM)

It is a non-invasive technique that allows the evaluation of signs of ocular surface damage in DED at a cellular level. It useful in assessing decreased corneal and conjunctival epithelial cell density, conjunctival squamous metaplasia, and corneal nerve changes like decreased sub-basal nerve density, increased tortuosity and more.(90-95)

4. Ocular surface sensitivity

Decreased or loss of corneal sensation leads to corneal epithelial disorders to neurotrophic keratopathy. The techniques used are classical Cochet-Bonnet which uses a nylon filament in varying length for applying different intensities or non-contact air-jet esthesiometers(CRCERT-Belmonte esthesiometer) to evaluate ocular surface sensitivity.(96,97)

Tests for assessing the inflammation of the ocular surface:

Inflammation is an important component of the pathophysiological mechanism of DED and a stable indicator of DED severity.Rapid testing for several inflammatory markers in DED have been developed in recent years. The most important are Matrix Metalloproteinase (MMP-9), Th1 and Th17 subclasses of cytokines, Tear chemokines such as CXCL9, -10, -11, and CXCR3 and others include the ocular surface immune markers. However these tests are not disease specific and the cost of these tests should be taken into account while advising. These tests are useful in the aspect of research in trials targeting for newer immunosuppressive medications for severe diseases.(98-100)

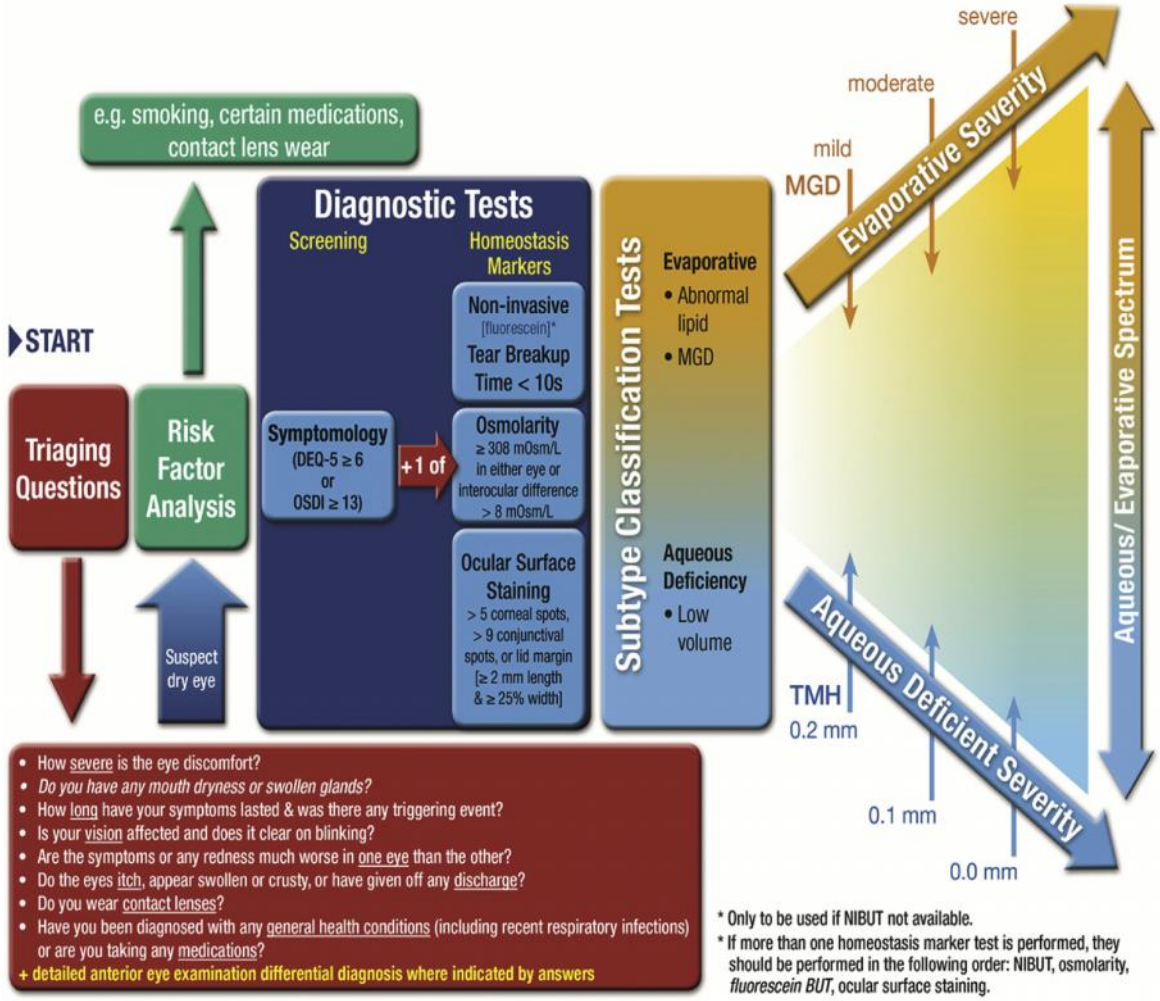
Tests for detecting eyelid signs

These tests are to classify subtype of DED and to apply appropriate management. The presence of blepharitis, amount of blink rate and completeness should be noted. Lipid thickness can be observed with interferometry and the pattern graded. Meibography performed along with duct observation and expressibility would also be helpful (101)**.**

CLINICAL PROTOCOL FOR DRY EYE DIAGNOSTIC TEST BATTERY

According to the TFOS DEWS II diagnostic methodology subcommittee report the following test battery is recommended for diagnosis and monitoring for DED.

DED DIAGNOSTIC TEST BATTERY



The screening DEQ-5 or OSDI Questionnaire confirms that a patient might have Dry eye disease. The diagnostic testing includes non-invasive breakup time, osmolarity [measured prior to breakup time if FBUT used] and ocular surface staining with fluorescein and lissamine green (observing the cornea, conjunctiva and eyelid margin).

It is important to exclude conditions that forms differential diagnosis of dry eye disease with the help of the triaging questions and also to assess the risk factors which may indicate specific management.

Marked symptoms in the absence of clinical signs might indicate neuropathic pain. DED is a usually a subset of OSD. Presence of only signs in the absence of symptoms still warrants management to prevent DED manifestations and to prepare the optical corneal surface prior to refractive surgery or contact lens wear.

MGD features, lipid thickness/dynamics, and tear volume assessment, and their severity inform the subtype classification of DED as predominantly evaporative or predominantly aqueous deficient which helps deciding the effective management of DED. In accordance with the recommendations of the MGD Workshop (2011),

MILD MGD is indicated by a secretion grade 4-7, an expressibility grade of 1 and an amorphous/color fringe lipid pattern.

MODERATE MGD is indicated by meibomian gland orifice plugging, lid margin vascularity, a secretion grade 8-12, an expressibility grade of 2 and a meshwork or wave (flow) lipid pattern.

SEVERE MGD is indicated by lid margin meibomian gland orifice drop-out or displacement, a secretion grade > 13, an expressibility grade of 3 and an absent, globular or abnormal color fringe lipid pattern. Sjogren syndrome should be suspected if the DEQ-5 score is > 12.

MANAGEMENT AND THERAPY

Management algorithms are often proposed to recommend a sequence of treatments depending on the stage of disease, but as the disease often varies from patient to patient, both in severity and in character the treatment options have to be specific for each patient. The recommended protocol as per the DEW II management and therapy subcommittee is given below,(102)

Recommendations for the staged management and treatment of DED:

Step 1:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment

- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:

If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)

- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DEDd
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:

If above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops

- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses

Step 4:

If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

DIABETES AND DRY EYE:

Diabetes leads to significant ocular conditions, the most important is the retinopathy changes which is said to correlate with the duration of diabetes and the control of the diabetes. Besides retinopathy, diabetes can lead to other significant effects in the eye such as refractive changes, cataracts, glaucoma, nerve palsies and dry eye. Among these dry eye is one of the commonest complication associated with diabetes.

Pathophysiology of dry eye in diabetes

The prevalence of dry eye in diabetics has been reported to vary between 52-54 %.(109) Several theories have been proposed for the cause of dry eye in diabetics. The most important factors associated are:

Peripheral neuropathy secondary to hyperglycemia- Hyperglycemia results in damage to the peripheral nerves and their signaling pathways leading to complications like numbness, burning pain or even gangrene and life threatening complications. In the cornea sustained hyperglycemia along with the microvascular damage to the corneal nerves leads to blockage of the feedback mechanism that controls the tear secretion.(103) The lacrimal gland secretion is affected due to disruption in the innervation of the ocular surface. The greater the degree of diabetes, there

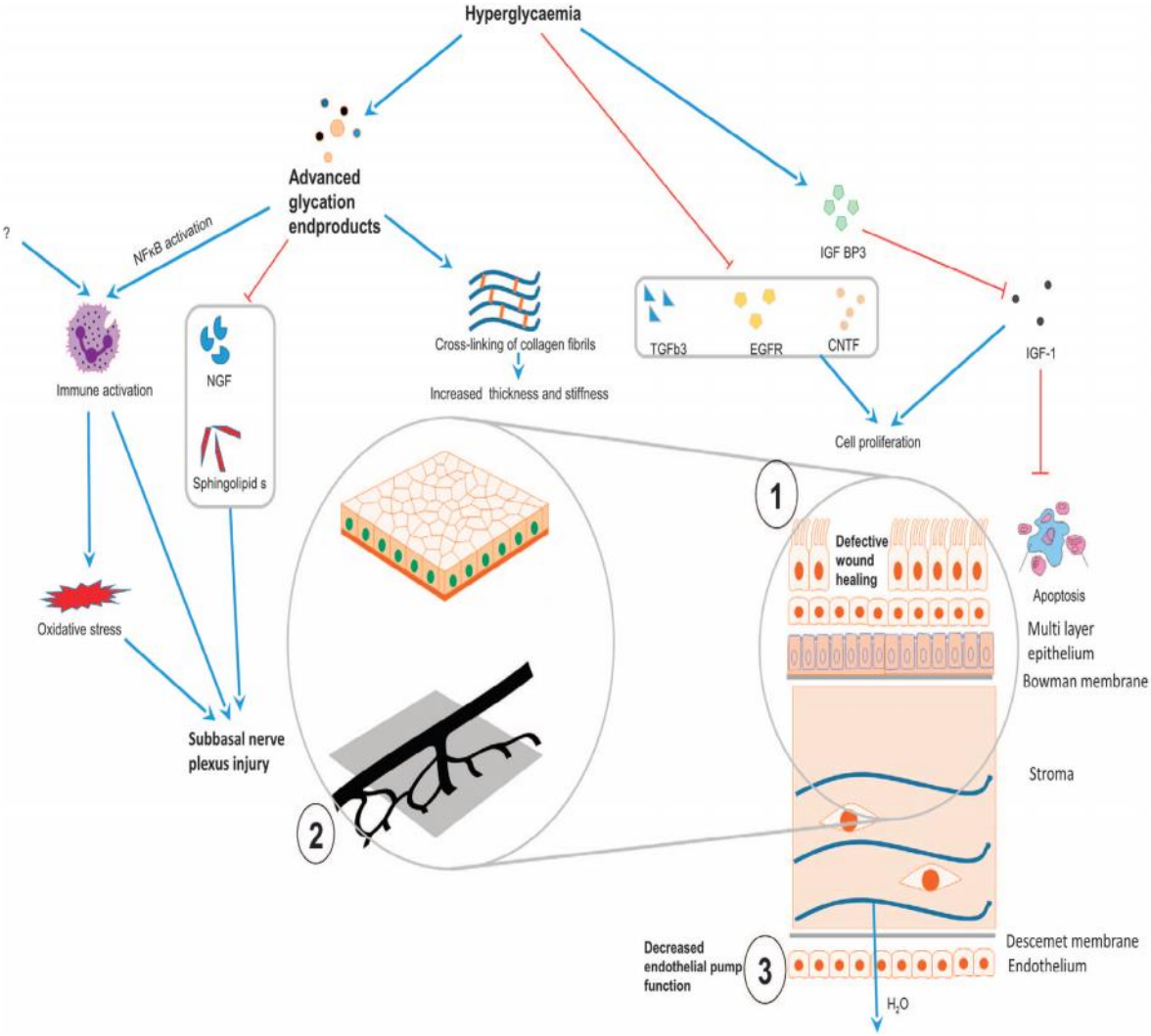
is increased tortuosity of the corneal nerves which results in alteration in the degree of corneal nerve degeneration in diabetes.(104)

Insulin insufficiency- Insulin exerts important effects on corneal and lacrimal gland metabolism, proliferation of the epithelial cells and their growth. A low insulin level in diabetes disturbs the biomechanical balance of these tissues and results in dryness. (103)

Inflammation – Hyperglycemia leads to inflammatory alterations which inturn impairs the normal tear secretion.(105) Lacrimal gland inflammation triggered by hyperglycemia results in lacrimal insufficiency or aqueous deficient dry eye.

Exposure of diabetic corneas to increased glucose concentration results in accumulation of advanced glycation end products,on the basement membrane lamina.(106) The MMP overexpression occurs in diabetic corneas which leads to recurrent erosions in these patients. Diabetes and dry eye are more likely to increase the probability of cornea ulceration than with either one condition alone.(107)

Schematic diagram showing pathogenesis of corneal disease in diabetes mellitus.



Symptomatology:

The most common symptoms of dry eye in diabetics are burning and foreign body sensation. Other findings include tear film instability, high grade conjunctival squamous metaplasia, reduction in the goblet cell density, decreased corneal sensation and a reduced lipid layer of the tear film.(105).

Types of dry eye in diabetes:

Most studies suggest aqueous deficiency is the most common type in diabetes due to the lacrimal gland insufficiency and diabetic neuropathy blocking the neural pathways for secretion. While some studies postulate that hyperglycemia on impairing inflammatory response leads to bacterial invasion causing blepharitis and thereby causing evaporative dry eye.(108)

STUDIES:

Manaviat et al studied the prevalence of dry eye and diabetic retinopathy (DR) in type 2 diabetics with 199 subjects, among whom 108 patients (54.3%) suffered from dry eye syndrome. Although dry eye syndrome was more common in older and female patients, this association was not significant. But there was significant association between dry eye syndrome and duration of diabetes (P = 0.01).Dry eye syndrome was more frequent in diabetic patients with DR (P = 0.02). DR was found in 140 patients (70.35%), which included 34 patients (17.1%) with mild non proliferative DR (NPDR), 34 patients (17.1%) with moderate NPDR, 22 patients (11.1%) with severe NPDR and 25 patients (25.1%) with proliferative DR (PDR).They concluded that there was significant relation between age, sex, duration of diabetes ,DR and dry eye(109).

Kaiserman et al compared the prevalence of keratoconjunctivitis sicca (KCS) in a prospective cohort of 22,382 diabetic patients with that in the general population. After age and gender adjustment, a significantly higher percentage of diabetic patients (20.6%) received ocular lubrication, compared with nondiabetic patients (13.8%, $P < .001$). The difference was significant for all age groups and for both sexes ($P < .001$). A similar significant difference was prominent between diabetic and nondiabetic patients aged 60 to 89 years who were frequent users of ocular lubrication**.** Ocular lubrication consumption increased with poorer glycemic control (mean annual HbA1c levels). Multivariate analysis revealed this effect to be independent of age, sex, place of birth, or place of residence.They concluded KCS is significantly more common among diabetic patients. Poor glycemic control correlates with increased artificial tear use in diabetic patients. (110)

Seifart et al conducted a study on dry eye syndrome and diabetes mellitus.92 patients with diabetes types I and II and aged from 7 to 69 years were compared with a group of normal healthy controls comparable in number, age and sex. The main points of comparison were subjective complaints, objective findings on conjunctiva and cornea, break-up time (BUT), basal secretion test, impression cytology of the conjunctiva, and grade of diabetic retinopathy. The results show that 52.8% of all diabetic

subjects complained of dry eye symptoms, as against 9.3% of the controls. A BUT value lower than 10 s was found in 94.2% of the diabetics and in only 5.8% of the controls. Basal secretion test lower than 5 mm was observed in 26% of the diabetics and in 16% of the normal controls. Pathologic conjunctival epithelium (grade III-V after Tseng) was found in 86% of the diabetic patients and in 6.7% of the healthy subjects. Among the type II diabetic patients, 70% had proven dry eye syndrome, while 57% with type I diabetes suffered from this. A positive correlation was found between the HBA1c values and the presence of dry eye syndrome. Impression cytology was found to give the most distinctive and discriminating results.(111)

Goebbels et al assessed the tear secretion and tear film function in 86 insulin dependent diabetics with retinopathy and 84 non-diabetic controls (age and sex matched).They performed fluorophotometry of tear secretion, the Schirmer test, and impression cytology of the conjunctival epithelium and determined the tear film break up time and compared with the healthy control group diabetics which showed decreased Schirmer test readings (-37%, $p < 0.001$) and significantly more frequent and pronounced signs of conjunctival metaplasia.In insulin dependent diabetics, reflex tearing was demonstrated to be significantly decreased. In contrast, unstimulated

basal tear flow and tear film break up time were found to be normal. However, a majority of insulin dependent diabetics showed distinct signs of conjunctival surface disease.(112)

Nepp et al studied the correlation between the severity of Diabetic Retinopathy and Keratoconjunctivitis Sicca. Patients with diabetic retinopathy (DR) seldom report symptoms of ocular surface irritation, but evaluations of dryness are pathologic.The study included 144 eyes of 72 patients. Severity of retinopathy was graded according to the Early Treatment Diabetic Retinopathy Study. The examinations for dry eyes included Schirmer's test, break-up time, lipid layer thickness, fluorescein and rose bengal staining of the cornea, impression cytology, and a questionnaire. A sicca severity score was calculated using a point system of the results of these tests. The score of those patients with mild to moderate retinopathy was compared to that of patients with severe to proliferative disease. There was a significant statistical difference in the sicca severity score between both groups, ($p < 0.006$. Student t test). (113)

JUSTIFICATION FOR THE STUDY

Few numbers of studies have been done regarding the tear film abnormalities in diabetics and decrease in tear production has been reported, but the overall data is inconclusive. Moreover, the ocular surface examination is usually ignored in diabetics and much importance is given to diabetic retinopathy in routine practice. Hence the present study is undertaken to evaluate the amount of tear production, the stability of the tear film and the condition of the ocular surface in diabetic individuals in order to detect possible ocular surface disease and its association with diabetic retinopathy.

AIMS AND OBJECTIVES

1) To evaluate the dry eye status in patients with type II diabetes.

2) To study the association between dry eyes and retinopathy in patients with type II diabetes.

MATERIALS AND METHODS

MATERIALS AND METHODS

- This was a hospital-based cross-sectional study which included patients with Type 2 Diabetes Mellitus who were attending the Ophthalmology Department in PSG Institute of Medical Sciences and Research, Coimbatore.

- The study was done spanning over a period of 18 months from January 2016 to June 2017.

- A convenient sample of 100 patients with type II diabetes and 100 matched controls were chosen

Inclusion criteria:

- Type II diabetic patients who attended the ophthalmology OPD in PSG Hospitals.

- Age and Sex matched non diabetic controls have been recruited from healthy volunteers.

Exclusion criteria:

- Patients on systemic medications such as antihistamines, tricyclic antidepressants, oral contraceptives and other medications which are known to cause dry eye.
- Contact lens users
- Patients who have undergone ocular surgery (LASIK/intraocular).
- Patients having local or systemic conditions other than diabetes mellitus known to cause dry eye.
- Smokers

METHODOLOGY:

After clearance from the Institutional Ethical Committee in accordance with the guidelines of the Declaration of Helsinki and taking informed consent, detailed history of each patient was obtained regarding the age, sex, occupation and presenting symptoms, duration, progression and associated conditions. Detailed history regarding diabetes such as type, duration, type of treatment, HbA1c values, FBS and PPBS levels were recorded.

Ocular surface disease index (OSDI) questionnaire was used to score the dry eye symptoms. It consisted of 12 questions which were grouped under 3 subsets: visual disturbance, visual function and environmental triggers. Score of maximum 4 was given for each question based on the severity of the symptom and subtotal for each subset calculated. The subtotal scores were added to get the total score and the OSDI was calculated using the formula OSDI = (total score) x 25 the whole divided by the number of questions answered. Using the OSDI score the patients were categorized as normal(0-12), mild dry eye(13-22), moderate dry eye(23-32) and severe dry eye(33-100).

Ocular examination included recording best corrected visual acuity and detailed anterior segment examination under slit lamp. The dry eye was detected by measuring tear film breakup time (TBUT), ocular surface dye staining pattern with fluorescein and schirmer's test.

TBUT test was performed by staining the tear film using a fluorescein impregnated strip without using topical anesthesia and asking the subjects to blink three times and then cease blinking until instructed. The tear film was observed using a slit lamp with blue cobalt filter. The time interval between the last blink and the appearance of the first random corneal dry spot in the tear film was measured. A value <10

seconds was considered abnormal. TBUT results graded as >10 secs – normal, 6-10 secs – mild to moderate, and <6 secs – severe.

Ocular surface staining was evaluated by staining the cornea with fluorescein. The staining area was graded using the Oxford Scheme on a numerical scale of 0–5 for the entire ocular surface based on comparison to the standard panel, with 0 representing equal to or less than panel A, 1 representing equal to or less than panel B but greater than panel A, 2 representing equal to or less than panel C but greater than panel B, 3 representing equal to or less than panel D but greater than panel D, 4 representing equal to less than panel E but greater than panel C, 5 representing greater than panel E. The severity was graded based on the score as 0-1 as normal, 2 as mild, 3- moderate and >4 as severe.

Schirmer test was performed without topical anesthesia using standardized Whatman filter paper 41. The strips were placed in the lower fornix away from the cornea and left in place for 5 min with the patient opened eyes. The wetting distance was measured in millimeters, and a reading <10 mm was considered abnormal.

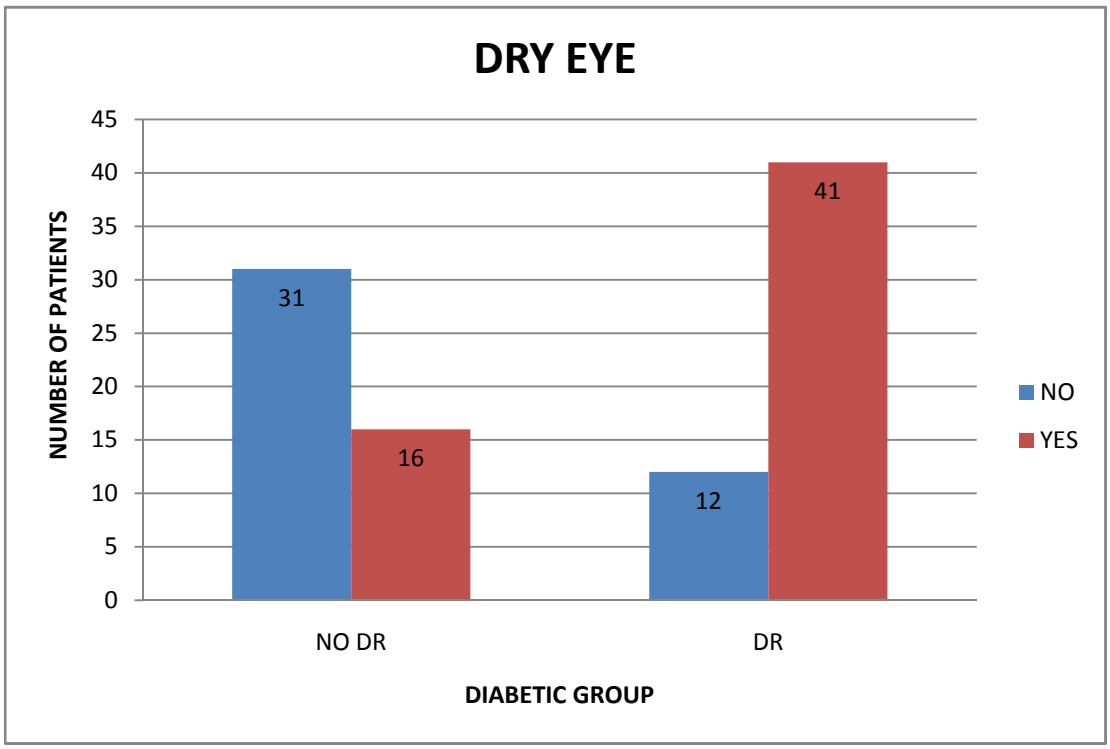
Retinal status evaluation done by slit lamp bimicroscopy using 90D lens after puppilary dilation. Diabetic retinopathy was graded according to Early Treatment Diabetic Retinopathy Study (ETDRS) criteria.

Statistical analysis

Statistical analysis was performed using SPSS version 19. The baseline characteristics of patients were presented as mean±standard deviation and n (%). Data on the patient's clinical characteristics were compared using One-way Analysis of Variance (ANOVA) as well as an independent sample Student's t-test and Chi-square test was used to see the comparison between the proportions. All tests for statistical significance were two-tailed, and performed assuming a Type I error probability of <0.05.

OCCURRENCE OF DRY EYE IN DIABETICS

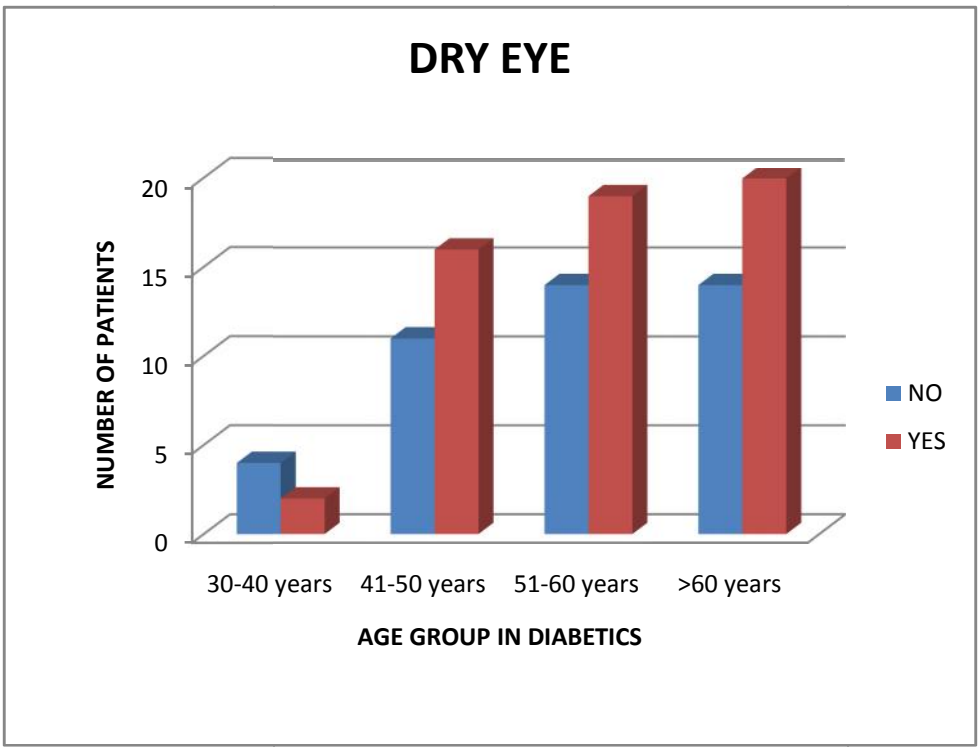
		Dry eye		Total	Chi-square statistics
		No	**Yes**		
Diabetic With No Retinopathy	N	31	16	47	
	%	66.0%	34.0%	100.0%	
Diabetic with Retinopathy	N	12	41	53	**19.069**
	%	22.6%	77.4%	100.0%	**(p=.000)**
Total	N	43	57	100	
	%	43.0%	57.0%	100.0%	



Among 100 patients with diabetes, 57 patients were diagnosed to have dry eye. Out of 47 patients without retinopathy, 16 patients (34%) were found to have dry eye and out of 53 patients with retinopathy, 41 patients (77.4%) had dry eye.

AGE DISTRIBUTION OF DRY EYE IN DIABETICS

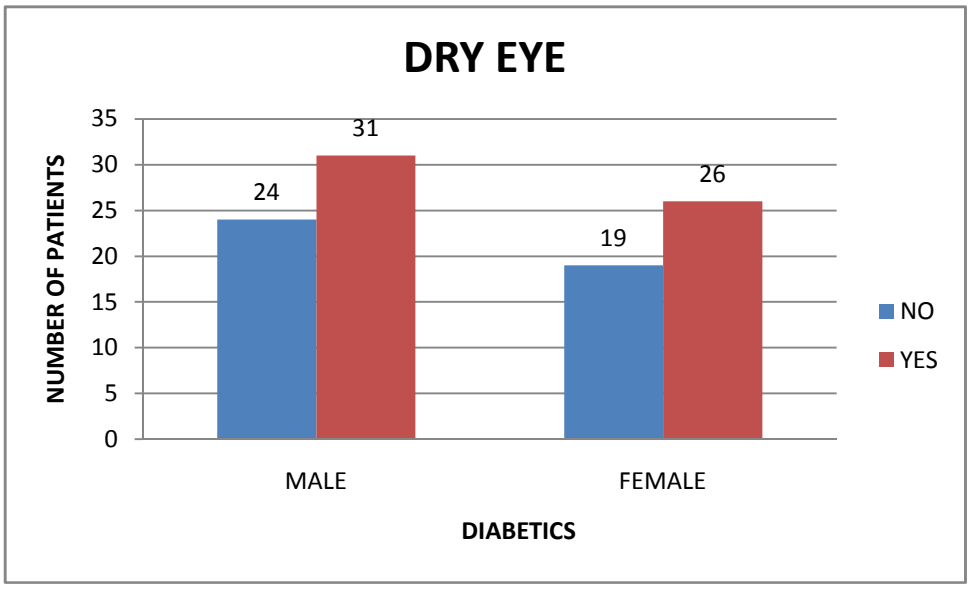
			Dry Eye		Total
			No	Yes	
Age	30-40 years	N	4	2	6
		%	66.67%	33.33	100.0%
	41-50 years	N	11	16	27
		%	40.74%	59.26%	100.0%
	51-60 years	N	14	19	33
		%	42.42%	57.58%	100.0%
	Above 60 years	N	14	20	34
		%	41.17%	58.83%	100.0%
Total		N	43	57	100
		%	43.0%	57.0%	100.0%



The mean age of diabetics without dry eye was 54.77 ± 9.82 years and the mean age of diabetics with dry eye was 56.49±9.32 years. As the age increased, the occurrence of dry eye also increased significantly. Out of 34 patients in the age group more than 60 years, 20 patients (58.83%) had dry eye.

SEX DISTRIBUTION OF DRY EYE IN DIABETICS

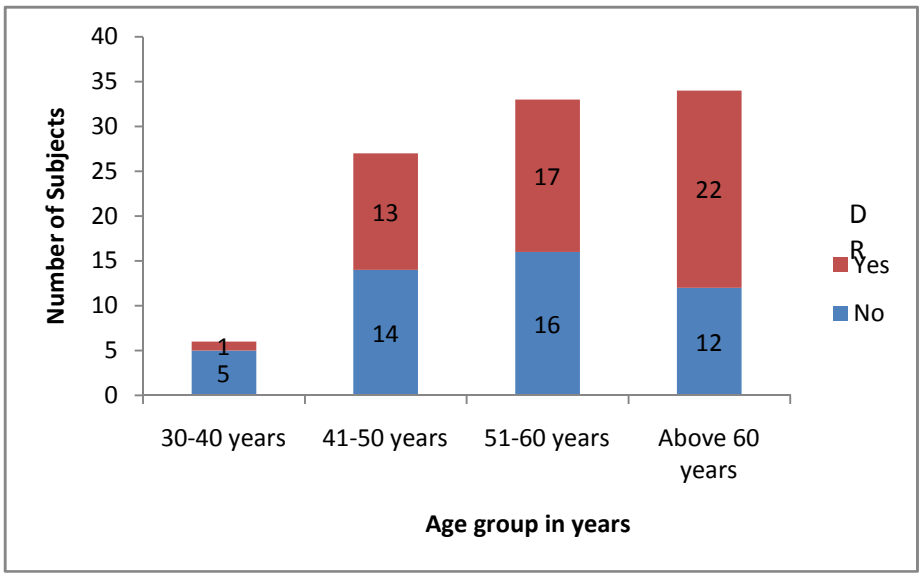
			Dry Eye		Total
			No	Yes	
Gender	MALE	N	24	31	55
		%	43.63%	56.37%	100.0%
	FEMALE	N	19	26	45
		%	42.22%	57.78%	100.0%
Total		N	43	57	100
		%	43.0%	57.0%	100%



Of the 100 consecutive patients included in the study, 55 were male and 45 were female. Among 55 male patients, 31 patients(56.37%) had dry eye and among 45 females patients, 26 patients(57.78%) had dry eye symptoms.

AGE DISTRIBUTION AMONG DIABETIC PATIENTS

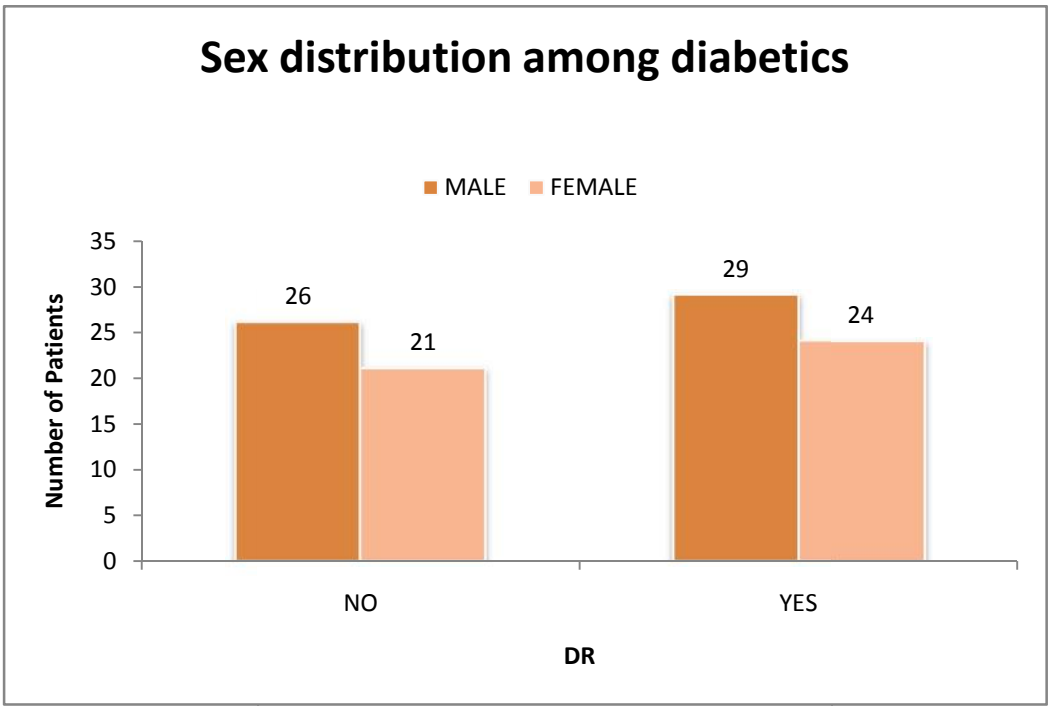
			Diabetic Retinopathy		Total
			No	Yes	
Age in years	30-40 years	N	5	1	6
		%	83.3%	16.7%	100.0%
	41-50 years	N	14	13	27
		%	51.9%	48.1%	100.0%
	51-60 years	N	16	17	33
		%	48.5%	51.5%	100.0%
	Above 60 years	N	12	22	34
		%	35.3%	64.7%	100.0%
Total		N	47	53	100
		%	47.0%	53.0%	100.0%



Mean age in diabetic patients without retinopathy was 53.72 ± 9.88 years, while in diabetic patients with retinopathy was 57.55 ± 8.93 years. With increasing age, the number of patients with diabetic retinopathy also increased significantly. Out of 34 patients in the age group more than 60 years, 24 patients (64.7%) had retinopathy of some degree.

SEX DISTRIBUTION AMONG DIABETIC PATIENTS:

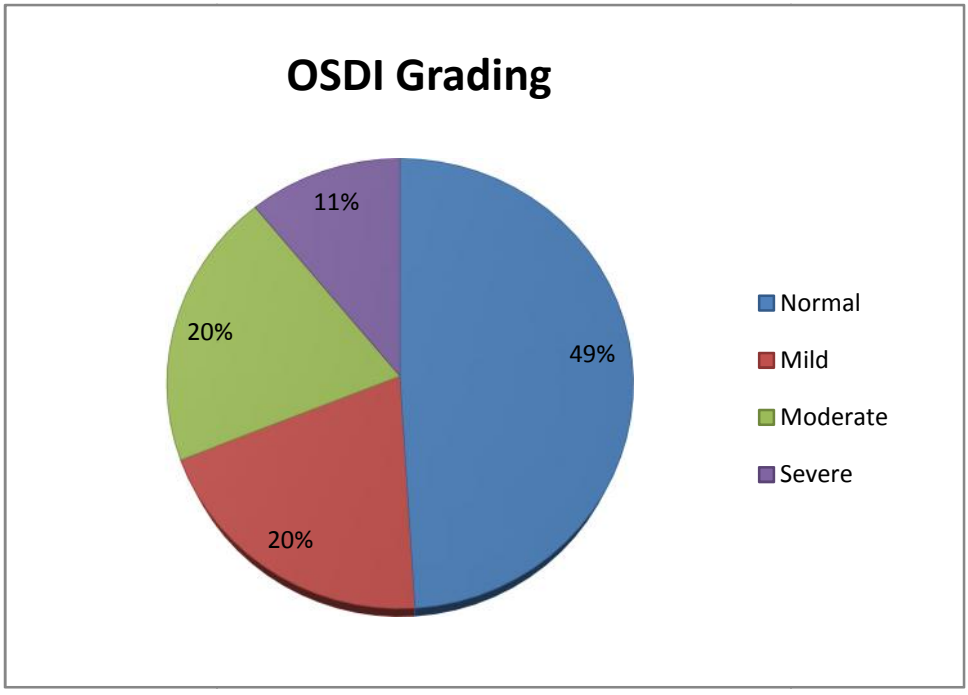
			Diabetic Retinopathy		Total
			No	Yes	
Sex	Male	N	26	29	55
		%	47.3%	52.7%	100.0%
	Female	N	21	24	45
		%	46.7%	53.3%	100.0%
Total		N	47	53	100
		%	47.0%	53.0%	100.0%



Of the 100 consecutive patients included in the study, 55 were male and 45 were female. Among 55 male patients, 26 patients(52.7%) had diabetic retinopathy and among 45 female patients, 24 patients(53.3%) had diabetic retinopathy.

DRY EYE AMONG DIABETICS BASED ON OSDI:

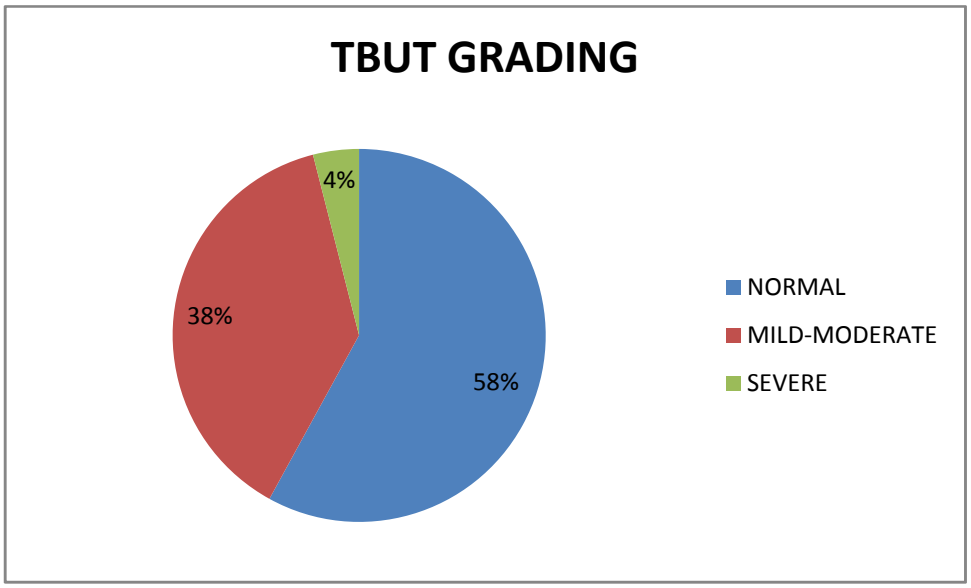
OSDI GRADING	NO. OF PATIENTS
Normal	49
Mild	20
Moderate	20
Severe	11
Total	100



Based on OSDI Questionnaire, 51% of patients had symptomatic dry eye. 20% of patients had mild dry eye, 20% had moderate dry eye and 11% had severe dry eye symptoms.

DRY EYE AMONG DIABETICS USING TBUT:

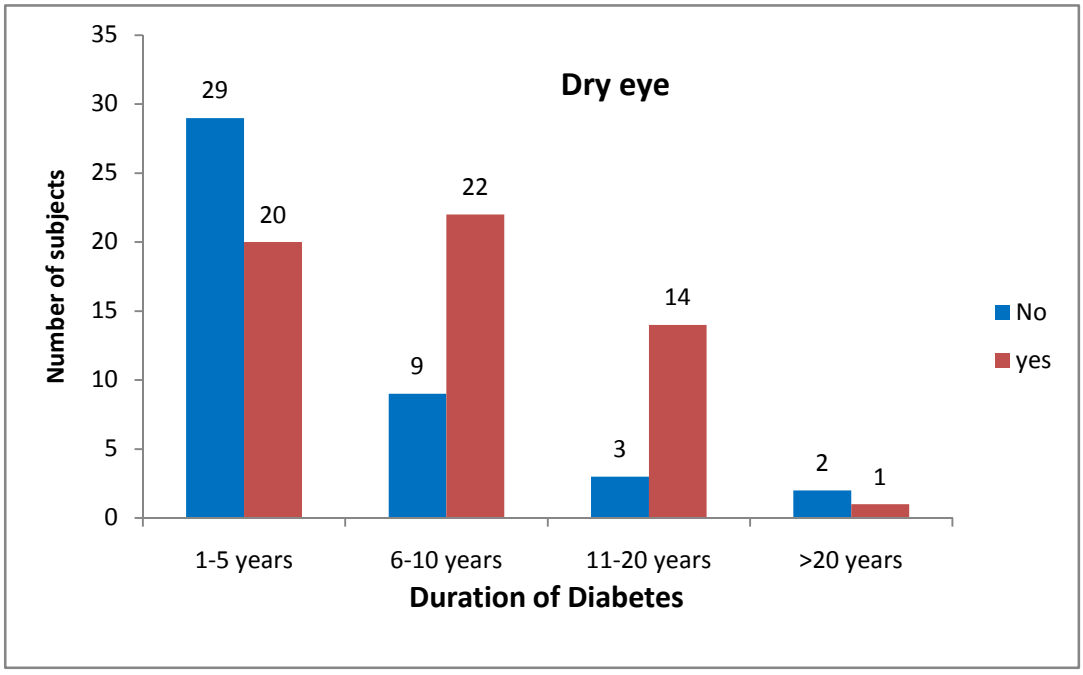
TBUT GRADING	NO. OF PATIENTS
NORMAL	58
MILD-MODERATE	38
SEVERE	4
TOTAL	100



T BUT was abnormal in 42% of diabetics. Among them 38% had mild-moderate values while severe dry eye was found in 4% of patients.

ASSOCIATION OF DRY EYE WITH DURATION OF DIABETES:

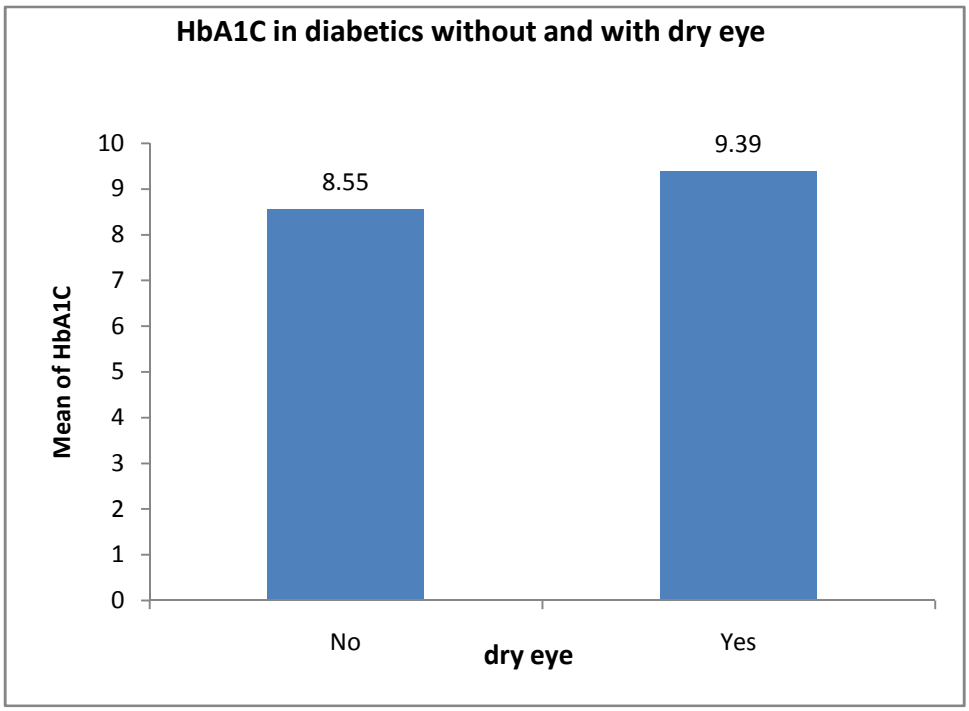
			Dry eye		Total	Chi-square statistics
			No	Yes		
Duration of diabetes	1-5 years	N	29	20	49	12.847** (p=.005)
		%	59.2%	40.8%	100.0%	
	6-10 years	N	9	22	31	
		%	29.0%	71.0%	100.0%	
	11-20 years	N	3	14	17	
		%	17.6%	82.4%	100.0%	
	>20 years	N	2	1	3	
		%	66.7%	33.3%	100.0%	
Total		N	43	57	100	
		%	43.0%	57.0%	100.0%	



Significant Association between diabetic duration and Dry eye was observed ($p < 0.05$), Occurrence of dry eyes was 71% in diabetics with duration more than 6 years and 82.4 % in diabetes with duration more than 11 years.

ASSOCIATION OF DRY EYE WITH HbA1c LEVELS IN DIABETICS:

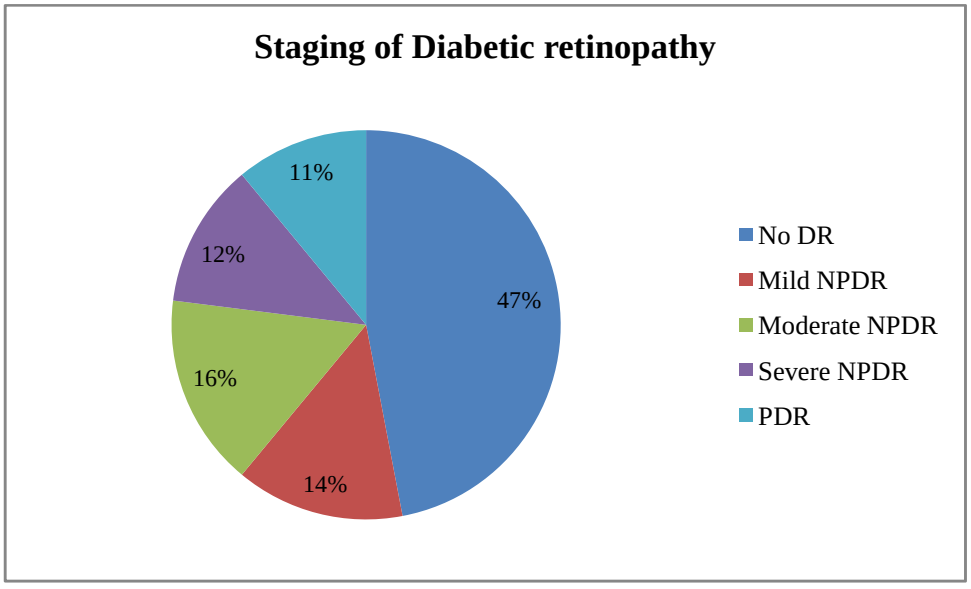
	Dry eye	N	Mean	SD	t-value
HbA1C	No	43	8.55	2.31	**1.808**
	Yes	57	9.39	2.29	**(p=.074)**



The mean HbA1c values of diabetics with and without dry eye were 8.85±2.41 and 9.20±2.27 respectively. There was no significant association between the HbA1c levels and the dry eye status in diabetics (p-value = 0.074).

STAGING OF RETINOPATHY IN PATIENTS WITH TYPE II DIABETES:

STAGING	No. of patients
No DR	47
Mild NPDR	14
Moderate NPDR	16
Severe NPDR	12
PDR	11
Total	100



In our study, 47% of patients had no signs of retinopathy, 14 % had mild non proliferative diabetic retinopathy (NPDR), 16% had moderate NPDR, 12% had Severe NPDR and 11% had Proliferative diabetic retinopathy (PDR).

CLINICAL CHARACTERSTICS OF STUDY POPULATION:

Characteristic	Study group					
	Control group (n=100)		Diabetic with no retinopathy (n=47)		Diabetic with Retinopathy (n=53)	
	Mean	SD	Mean	SD	Mean	SD
Age (yr)	54.7	10.23	53.72	9.88	57.55	8.93
DM_duration (yr)*	-	-	4.86	5.23	8.79	5.53
HbA1C(%)	-	-	8.85	2.41	9.20	2.27
Schirmer (mm)*	24.15	5.15	11.67	4.41	10.04	3.42
TBUT(sec)*	14.65	3.68	13.94	4.66	11.44	4.23
OSDI*	6.98	6.52	8.04	8.26	21.37	12.16

DM:Diabetes mellitus, TBUT:Tearfilm breakup time, OSDI:Ocular surface disease index

* p-value < 0.05

The mean age of subjects in the control group was 54.7± 10.23 years, in diabetics without retinopathy was 53.72±9.88 years and in diabetics with retinopathy was 57.55±8.93 years. The mean duration of diabetes in patients without retinopathy was 4.86±5.23 years while the duration of diabetes in patients with retinopathy was 8.79±5.53 years.

The mean HbA1c values of diabetics with and without retinopathy were 8.85±2.41% and 9.20±2.27 % respectively. There was no siginificant association between the HbA1c levels and the dry eye status in diabetics (p-value = 0.074).

The mean schirmer test value in control group was 24.15±5.15 mm, in diabetics without retinopathy was 11.67±4.41 mm and in diabetics with retinopathy was 10.04±3.42 mm.

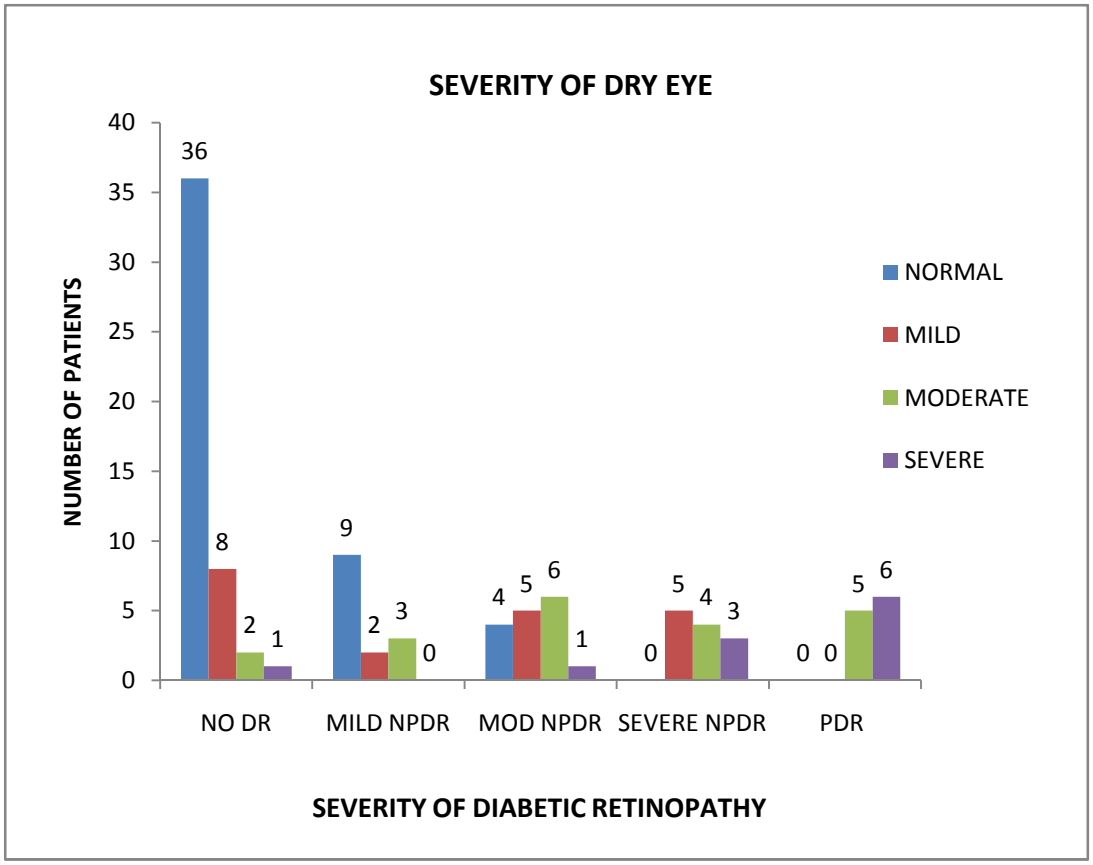
The mean TBUT value in control, diabetics without retinopathy and diabetics with retinopathy were 14.65±3.68 secs, 13.94 ± 4.66 secs and 11.44±4.23 secs respectively. There was significant difference in the TBUT values between all the three groups with the lower values in the diabetic retinopathy group.

The mean OSDI score in control group was 6.98±6.52, in diabetics without retinopathy was 8.04±8.26 and the diabetics with retinopathy was 21.31±12.16. Significant difference was noted between the control and diabetics with retinopathy group (p-value=0.00) while no significant difference was noted between the control group and the diabetics without retinopathy.

TABLE SHOWING ASSOCIATION BETWEEN DRY EYE AND SEVERITY OF DIABETIC RETINOPATHY:

Diabetic retinopathy(DR)		Ocular surface staining				Total	Chi-square value
		NORMAL	MILD	MOD	SEVERE		
NO DR	N	36	8	2	1	**47**	
	%	76.60	17.02	4.26	2.13	**100**	
MILD NPDR	N	9	2	3	0	**14**	
	%	64.29	14.29	21.43	0	**100**	
MOD NPDR	N	4	5	6	1	**16**	**78.730****
	%	25.00	31.25	37.50	6.25	**100**	**(p= .000)**
SEVERE NPDR	N	0	5	4	3	**12**	
	%	0.00	41.67	33.33	25.00	**100**	
PDR	N	0	0	5	6	**11**	
	%	0.00	0.00	45.45	54.55	**100**	
Total	N	**49**	**20**	**20**	**11**	**200**	

There was significant association found between dry eye status and diabetic retinopathy ($p<0.01$). More cases in Diabetic Retinopathy group reported with moderate and severe dry eye. The percentage of patients having dry eye among patients with no diabetic retinopathy was 23.41% as against and 35.72% in mild NPDR, 75% in moderate NPDR, 100% in severe NPDR and PDR patients respectively. All the patients with severe NPDR and PDR had some form of dry eye.


SEVERITY OF DRY EYE
NUMBER OF PATIENTS
40
35
30
25
20
15
10
5
0
36
8
2
1
9
2
3
0
4
5
6
1
0
5
4
3
0
0
5
6
NO DR
MILD NPDR
MOD NPDR
SEVERE NPDR
PDR
NORMAL
MILD
MODERATE
SEVERE
SEVERITY OF DIABETIC RETINOPATHY

DISCUSSION

Our study shows that abnormal OSDI scores, TBUT, Schirmer test and ocular surface staining were noted in diabetic patients compared to controls. These observations indicate that dry eye is a significant factor responsible for ocular surface disease in diabetics. Moreover, a positive association was noted between dry eye status and severity of diabetic retinopathy.

In our study the prevalence of dry eye in diabetics was 57%. In particular, diabetics with retinopathy, had higher prevalence(77.4%) of dry eye than diabetics without retinopathy .Similar to our study Seifart et al found 52.8% of diabetics had dry eye symptoms among 92 patients included their study.(113) Adequate glycemic control could prevent dry eye disease as well as retinopathy progression in diabetics. However their study included both type I and type II diabetics. High prevalence could be attributed to reduced tear secretion in DM patients caused by autonomic dysfunction in these patients. The tropical and dry climate in our region would be an added factor for the increased prevalence of dry eye in our study.

In our study, the mean age of diabetics with dry eye was 56.49±9.32 years. Dry eye was more prevalent in patients aged over 50 years showing a significant association between the age and dry eye.

Of the 100 consecutive patients included in the study, 55 were male and 45 were female. Among 55 male patients, 31 patients(56.37%) had dry eye and among 45 females patients, 26 patients(57.78%) had dry eye symptoms. There was a slightly higher preponderance among female patients which could be attributed to thinner lipid layer of the tearfilm of the females.

We also found a significant association between dry eye disease and the duration of diabetes in our study. Longer the duration of diabetes, higher was the prevalence of dry eye disease. About 71% of patients with duration of diabetes more than 6years had dry eye symptoms. 82.5 % of diabetics with more than 11 years of diabetes had dry eye symptoms.

In the present study, we found no significant association between the HbA1c levels and dry eye(p=0.074).This was in contrast to previous studies by Seifart et al who found a positive correlation between the HBA1c values and the presence of dry eye syndrome and Kaiserman et al, also found a higher use of artificial tears in diabetic subjects with a higher HbA1c levels.(111,110) Our observations are consistent with that of Fuerst et al who assessed the relationship between tear osmolarity and

dry eye symptoms in 50 diabetics and found no correlation in HbA1c levels with the dry eye disease.(114) This could be explained by the fact HbA1c levels reflect only the average blood glucose level over the previous 3 months. Hence, HbA1c levels may not necessarily correlate with dry eye and ocular surface abnormalities which occurs over years of poorly controlled diabetes.

Based on the OSDI symptom scores, among the 100 diabetic patients 51% of patients had symptomatic dry eye. Among them, mild dry eye was noted in 20% of patients, moderate dry eye in 20% of patients and 11% had severe dry eye. The frequency of dry eye symptoms in our study matched to that of Manaviat et al, who found that 54% of 199 diabetic subjects had dry eye symptoms.(109) Our study showed significant difference in the OSDI scores between the diabetics with retinopathy and the non diabetic group while no significant difference between the diabetics without retinopathy and the controls.

In our study, significant differences in TBUT and schirmer test was observed ($p<0.05$) among allthe study group with lower TBUT in patients with diabetic retinopathy. Abnormal TBUT value (<10 secs) was seen in 40% of the diabetic group. Schirmer test was abnormal (<10mm / 5min) in 54% of diabetic subjects. A study by Dogru et al also noted significantly reduced TBUT and Schirmer test values in diabetic patients

with peripheral neuropathy and poor metabolic control.(115) Presence of autonomic dysfunction, abnormalities in the tear film dynamics, decrease in corneal sensation , along with microvascular damage to lacrimal gland contribute to the increased prevalence of dry eye in diabetics.

Of the 100 patients with type 2 diabetes included in our study, diabetic retinopathy was detected in 53%. The results are consistent with the Wisconsin Epidemiological Study for Diabetic Retinopathy conducted in the USA which studied 1313 subjects and reported 50.3% had DR but this study included the type 1 diabetics too.(116).Ruta LM et al reviewed various epidemiological studies and reported the prevalence varied from as low as 10% to as high as 61% in known diabetic persons and from 1.5 to 31% in newly diagnosed persons. The median prevalence of any diabetic retinopathy in known diabetes was 27.9% (22-37%) with higher prevalence in developing countries.(117)

In our study, the mean age in diabetic patients without retinopathy was 53.72 ± 9.88 years, while in diabetic patients with retinopathy was 57.55 ± 8.93 years. With increasing age, the number of patients with diabetic retinopathy also increased significantly. 64.7 % patients aged above 60 years had some degree of retinopathy.

The male:female ratio was about 55:45 in the diabetic group. The percentage of females (53.3%) with diabetic retinopathy was slightly higher compared to males(52.7%).

We compared the dry eye status with the staging of retinopathy in diabetics and observed a significant association between dry eye and the severity of diabetic retinopathy ($p<0.05$). The proportion of patients with dry eye was significantly higher in patients with advancing grades of retinopathy. Several other studies have also reported a positive correlation between diabetic retinopathy and dry eye. Nepp et al found a significant statistical difference in the sicca severity score between patients with mild to moderate diabetic retinopathy and severe to proliferative disease.(113) Ozdemir et al and Yu L.et al reported a declined tear film function in the diabetics with PDR than in those with NPDR.(118,119)

Several mechanisms can account for the observed results in our study. Oxidative stress and inflammation are common underlying factors in the pathogenesis of dry eye as well as diabetic retinopathy. Progressive damage to corneal nerve fibres as a result of diabetic neuropathy can lead to impaired corneal sensation and dry eye which correlates with the severity of diabetic retinopathy.

CONCLUSION

- Patients with type II diabetes have higher prevalence of dry eye when compared to their age matched controls in our study.
- Evaluation of diabetic patients using the OSDI questionnaire can be helpful in identifying dry eye in early stages.
- Significant association was noted between dry eye disease and the duration of diabetes.
- No correlation was found between HbA1c levels and dry eye status in patients with diabetes.
- Significant reduction in TBUT and Schirmer test was found in diabetic patients, especially those with retinopathy.
- A positive association was observed between severity of retinopathy and dry eye.

Patients with advanced diabetic retinopathy are at increased risk of developing ocular surface complications. Hence our study insists that clinical evaluation of dry eye should be an integral part of ocular examination in diabetic patients.

LIMITATIONS

- Cross sectional design of the study
- Limited sample size
- Lack of more objective tests like conjuctival impression cytology and tear osmolarity measurement are limitations of our study.

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CASE PROFORMA

- NAME
- AGE
- SEX
- IP/OP NUMBER
- ADDRESS
- PRESENTING COMPLAINTS

HISTORY OF PRESENTING ILLNESS

- DURATION OF DIABETES
- SPECTACLE WEAR (DURATION, FOR NEAR OR DISTANT VISION)

PAST HISTORY

- OTHER OCULAR DISEASES
- OTHER CO-EXISTING SYSTEMATIC CO MORBIDITIES

OSDI QUESTIONNAIRE

TBUT SCALE

OCULAR SURFACE STAINING GRADE

SCHIRMER TEST GRADING

OPHTHALMIC EXAMINATION

- **VISUAL ACUITY(INCLUDING PIN HOLE)**
- **HEAD POSTURE**
- **FACIAL SYMMETRY**
- **EOM**

RIGHT EYE LEFT EYE

- **LIDS AND ADNEXA**
- **CONJUNCTIVA**
- **CORNEA**
- **SCLERA**
- **ANTERIOR CHAMBER**
- **IRIS**
- **PUPIL**
- **LENS**
- **VITREOUS**
- **IOP**
- **FUNDUS**
- **DETAILS OF INVESTIGATION DONE: HBA1C LEVELS**

MASTER CHART

S.No	OP /IP No	AGE	SEX	DM Duration	OSDI	Schirmer		TBUT		KES		DR	HbA1C
						RE	LE	RE	LE	RE	LE		
1	O17042831	55	M	1	5.5	13	8	13.11	13.71	1	0	0	6.9
2	O17053371	55	F	3	3.1	8	10	6.63	6.25	0	1	0	7.6
3	O17034527	54	F	1	9	0	3	6.02	6.02	1	0	0	7.9
4	O17040600	43	F	1	0	2	2	5	15.67	0	0	0	11.3
5	O12004626	43	F	6	7.5	13	9	10.65	16.65	0	1	0	6.8
6	O07013550	52	M	11	12.5	13	12	10.72	18.56	2	2	0	10.6
7	O17029213	45	F	1	20	12	11	8.52	10.72	2	2	0	7.3
8	O04010153	48	M	1	2.3	10	13	10	12.52	1	0	0	10.9
9	O17024311	53	M	1	11.36	9	10	15.76	14.69	0	0	0	11.3
10	O08021872	56	F	3	12.27	11	8	10	7.8	2	2	0	7.8
11	O05021945	62	M	20	10	9	7	12.62	13.46	0	1	1	7
12	O08039184	76	M	1	7.14	10	9	15.29	10.06	0	0	0	15.2
13	O17004644	75	F	5	8.3	9	8	13	12	1	0	2	7.7
14	O17021152	55	M	2	0	11	15	15.39	16.99	0	1	0	6.9
15	O17020226	60	M	10	41.7	11	8	6.8	8.07	4	4	0	15.6
16	O17016289	68	M	5	22.7	8	6	11.62	13.68	3	3	2	11
17	O13004530	48	M	1	11.36	0	0	6	8.23	1	1	0	10.4
18	O17006960	52	F	5	5.5	14	8	13.53	14.58	0	0	0	9.3
19	O16088307	42	M	5	34.09	8	8	10	6	5	5	3	14
20	O17004943	55	F	9	16.67	9	9	8.42	12.43	2	2	3	11.2
21	O15070604	59	F	1	13.89	9	5	4	5.8	2	2	0	7.6
22	O15079150	50	M	10	50	7	8	8	12	4	5	4	11.3
23	O16066297	65	F	20	42.85	9	10	8	9.5	4	4	3	8.6
24	O16051099	60	F	5	0	10	13	20	10	0	1	0	7.8
25	O16064404	55	F	1	0	12	11	8	15	0	0	0	7.56
26	O16067449	65	F	12	25	10	9	10	11	3	3	4	13

27	O16066843	65	M	15	22.22	11	10	10	6	3	3	0	8.9
28	O14068958	66	M	20	7.5	10	11	10	18	1	0	0	8.8
29	O97001385	57	F	15	4.5	9	10	12.18	17.16	0	0	1	7.4
30	O16073366	40	M	1	27.5	11	13	12	13	3	3	0	5.5
31	O16021635	51	F	10	27.5	9	8	20.67	28.23	3	3	1	7.8
32	O17048689	49	M	3	10	16	11	24	25.08	1	0	0	8.5
33	O02040942	57	F	6	18.75	14	12	7	5	2	2	0	10.6
34	O17027395	45	M	1.5	8.33	12	9	19.06	10.05	0	1	0	9
35	O98019981	44	F	6	15	11	9	25.38	22.36	2	2	0	11
36	O12007866	59	M	25	9	8	9	17.86	20.62	0	1	2	13.7
37	O16009726	49	M	10	6.25	7	6	6.07	8.84	0	0	0	9
38	O17053397	43	M	1	0	12	15	15.8	16	1	1	0	9.8
39	O13078315	77	M	1	13.89	14	12	13	15.25	2	2	0	6.7
40	O17056102	49	F	15	13.89	9	13	7.22	7.45	2	2	3	5.6
41	O17066003	40	M	4	12.5	10	8	10	13	2	2	3	12.9
42	O13090437	50	M	5	15	9	10	10.94	13.62	2	2	2	7.8
43	O16054656	64	M	2	22.7	9	8	12.16	14.42	3	3	3	9.7
44	O17025189	52	F	7	16.67	12	9	8	11	2	2	3	7.6
45	O17064327	46	F	1	7.14	15	12	15.29	13.08	0	0	0	13
46	O16050783	45	F	1	11.36	14	13	15.53	14.97	0	0	0	12.3
47	O16061638	67	M	12	12.5	16	14	10.76	18.54	2	2	0	7.3
48	O14012504	67	F	7	7.5	12	10	10.64	15.56	1	0	0	6.5
49	O17069821	62	M	6	27.5	7	8	10.45	9.8	3	3	2	7.7
50	O17035821	57	M	5	10	8	10	13.44	12.56	1	1	1	8.7
51	O17066524	62	M	8	25	11	8	10.67	8.02	3	3	2	8.9
52	O08077379	51	M	6	6.8	15	12	15.65	16.45	0	0	0	7.3
53	O17032118	61	F	7	18.75	10	11	7.8	5.2	2	2	2	10.2
54	O17031224	51	M	6	34.09	7	8	10.5	7.08	4	5	4	8.8
55	O00024886	78	M	15	32.5	8	9	6.07	10.2	4	4	4	10.7
56	O06020524	67	F	10	5.6	16	13	17.62	18.32	0	0	0	7.6
57	O16029085	60	F	6	10.2	10	9	20.76	24.32	1	1	1	6.7

58	O13071510	40	F	3	0	12	12	21.9	17.54	0	0	0	6.3
59	O12016723	50	M	5	25.2	11	7	13.32	12.02	3	3	3	8.2
60	O17056688	64	M	10	29.54	9	11	10	7.56	3	3	4	8.9
61	O14033474	62	M	8	0	13	14	12.88	17.89	1	1	0	7
62	O17056075	61	M	7	7.5	15	12	10.76	12.45	0	0	0	8
63	O05019509	53	M	8	31.18	8	11	6.07	8.38	3	3	4	12.1
64	O13022843	44	M	5	0	11	13	18.32	12.88	0	0	2	6
65	O15029314	61	F	6	8.33	10	12	20	22	0	1	1	7.8
66	O16004903	71	F	11	27.78	11	12	7.33	8.34	3	3	2	8.9
67	O17056576	52	F	2	3.1	9	12	6.66	6.52	0	0	1	8.2
68	O12058548	58	M	4	22.7	12	11	11.26	16.38	3	3	2	9.7
69	O06003668	52	F	4	11.11	11	12	13	11.9	0	0	1	9.6
70	O08068133	50	F	6	22.7	10	12	16.12	16.38	3	3	2	9.6
71	O17030556	40	F	1	0	12	14	15.87	19.72	1	0	0	7.1
72	O09046532	57	M	12	41.7	10	11	10	4	5	5	4	9.4
73	O17038744	50	F	6	25	11	13	8.07	6.8	3	3	4	13.2
74	O17030193	69	M	6	20.45	9	12	8.23	7.66	2	2	2	7.7
75	O17030153	65	M	2	5.5	12	14	15.33	14.69	0	0	0	5.4
76	O17055247	56	M	6	22.9	8	11	6.07	8.32	3	3	3	7.9
77	O17030466	48	M	4	0	17	18	18.89	17.53	0	1	0	9.8
78	O17026180	65	M	5	8.33	15	11	19.07	16.05	0	0	0	8.9
79	O11066763	63	F	5	0	7	11	18	20	1	0	1	8.3
80	O17030288	44	F	2	0	11	16	20	21	0	0	0	10.7
81	O14069491	53	F	8	3.1	8	10	16.66	12.64	0	1	0	9.7
82	O13071510	40	F	1	0	10	12	22	21.8	0	0	0	6
83	O17029477	67	M	13	46.8	11	8	7.73	9.5	5	4	4	12.3
84	O17029761	45	F	4	12.5	13	12	10	13	2	2	3	9.1
85	O17028456	45	M	5	5.5	11	12	15.43	18.45	1	0	2	6.5
86	O17028524	51	M	6	34.09	10	11	10	6.08	4	5	2	15.8
87	O17028330	66	M	3	5.5	12	9	13.88	15.84	0	1	1	7.6
88	O16086025	49	F	20	39.2	11	12	8.2	7.35	5	5	3	9.1

89	O02044819	63	M	25	10	12	11	12.64	18.36	0	0	0	7
90	O03007536	72	M	14	25	10	13	10	11.2	3	3	1	8.2
91	O11084068	66	M	21	15	12	11	12.09	18	2	2	2	5.8
92	O03033812	68	F	5	15	12	10	11.7	9.4	2	2	1	6.6
93	O17065252	60	F	6	18.75	12	12	7.6	5.9	2	2	1	7
94	O17036114	47	F	7	42.85	11	10	4.7	8.5	4	5	4	10.6
95	O16026308	69	M	12	25	12	15	10	11	3	3	4	7.9
96	O17052125	52	M	8	22.22	11	10	10	11	3	3	1	11
97	O08014677	37	M	1	0	12	14	18.4	22.75	1	0	0	6
98	O17035302	47	F	4	31.81	9	12	10	9.5	3	3	3	9.1
99	O17035144	60	M	5	0	13	8	15.56	16.48	1	0	0	13.5
100	O13046441	61	F	20	12.5	10	11	10.3	11.8	2	2	2	7.4

S.No	OP /IP No	AGE	SEX	OSDI	Schirmer		TBUT		KES	
					RE	LE	RE	LE	RE	LE
101	O16068246	57	M	16.67	24	30	11.43	12.68	0	0
102	O08019314	40	F	6.8	25	30	8.02	10.04	0	0
103	O17027888	60	F	15.63	30	30	12.68	13.42	0	0
104	O17027875	45	M	9.1	25	30	14.52	9.92	0	0
105	O14055883	43	F	25	30	20	20.05	18.26	0	0
106	O17047525	37	M	0	35	35	26.08	21.07	0	0
107	O17044023	53	F	0	10	15	18.35	15.65	0	0
108	O17046507	45	F	7.5	25	30	30	31	0	0
109	O17027967	40	M	13.64	15	10	20.4	17.86	0	0
110	O17021151	34	M	9.1	35	35	14	13.8	0	0
111	O17021132	50	M	6.8	25	20	12.8	11.82	0	0
112	O17021131	38	M	2.3	20	15	13	20	0	0
113	O160O2609	44	M	15.9	30	30	15.4	14.86	0	0
114	O17038167	45	M	2.27	25	30	15.26	18.36	0	0
115	O17055115	50	F	7.5	25	23	21.8	18.12	0	0
116	O17038460	48	M	7.5	25	30	22	20	0	0
117	O17038093	70	F	6.25	24	21	12.68	13.43	0	0
118	O17007348	61	F	15.63	21	19	21.8	23	0	0
119	O05017545	40	F	0	25	27	23	21.22	0	0
120	O17008208	52	M	6.8	25	20	13.9	14.53	0	0
121	O17069256	75	F	12.5	18	19	12.68	14.23	0	0
122	O17055113	60	F	5.5	22	18	18.64	16.72	0	0
123	O97025965	74	M	16.67	18	23	15.67	13.45	0	0
124	O97025966	74	F	11.11	17	25	23.8	24.55	0	0
125	O96005542	43	F	0	22	27	20.5	23.3	0	0
126	O17057173	60	M	0	30	30	21.43	19.81	0	0
127	O12050495	61	F	15.63	30	30	17.89	18.91	0	0
128	O14024350	58	F	5.5	25	23	18	17.53	0	0
129	O17069160	52	F	0	12	15	18.55	16.78	0	0

130	O11083082	70	M	14.28	15	18	17.84	19.2	0	0
131	O17038390	60	M	5.5	23	32	21	22.92	0	0
132	O17014979	65	F	11.11	28	26	13.67	14.86	0	0
133	O17050683	50	F	0	30	30	15.67	17.8	0	0
134	O17025189	52	F	0	24	28	12.56	13.78	0	0
135	O17064893	53	F	6.8	24	25	12.44	16.32	0	0
136	O17068894	75	F	12.5	14	18	12.68	11.72	0	0
137	O07017172	52	F	5.5	26	20	21.88	24.56	0	0
138	O17021119	48	M	5.5	25	30	19.8	16.76	0	0
139	O17021126	44	M	0	30	30	22.6	23.54	0	0
140	O17021117	49	M	6.8	25	20	21.58	18.12	0	0
141	O17021129	47	M	9.1	25	30	15.23	19.29	0	0
142	O17021134	45	M	7.5	25	30	20	21	0	0
143	O1703588	56	M	16.67	24	30	14.31	16.82	0	0
144	O17069951	59	M	16.67	28	32	13.14	12.86	0	0
145	O17038849	45	F	7.5	26	25	23	22.65	0	0
146	O17069833	62	M	15.63	30	30	16.82	14.32	0	0
147	O16001030	46	F	7.5	23	25	22	24.8	0	0
148	O17060133	67	F	12.5	17	19	15.9	17.5	0	0
149	O13034426	62	F	11.11	25	28	14.88	16.79	0	0
150	O17057628	40	F	0	30	30	16.8	18.54	0	0
151	O1502620	48	M	0	25	25	20.16	21.9	0	0
152	O17060137	57	M	0	23	21	15.8	16.9	0	0
153	O14023142	59	F	7.5	30	30	22.5	21.8	0	0
154	O16064196	65	M	5.5	20	18	15.56	15.43	0	0
155	O17069710	63	F	5.5	25	28	18.8	17.65	0	0
156	O07072077	59	M	11.36	24	22	15.4	16.5	0	0
157	O16068206	46	M	13.64	15	12	20.66	18.76	0	0
158	O17038557	53	M	0	20	25	18.53	16.55	0	0
159	O17065467	52	M	0	18	19	13.58	15.65	0	0
160	O07041260	68	F	7.5	16	15	16.7	18.42	0	0

161	O12084715	51	M	0	22	25	12.8	13.8	0	0
162	O17067120	45	F	0	23	28	13.34	11.98	0	0
163	O06040938	47	F	5.5	30	30	15.56	15.87	0	0
164	O15043027	67	F	15.9	30	30	15.4	14.86	0	0
165	O17048276	53	F	0	25	25	16.33	18.75	0	0
166	O16035618	48	F	0	23	28	17.8	15.67	0	0
167	O16060106	50	F	0	30	30	12.89	17.65	0	0
168	O14045870	60	F	13.88	18	20	18.6	14.23	0	0
169	O97006854	52	F	0	21	19	15.38	16.8	0	0
170	O17052191	60	M	14.58	24	30	14.33	18.26	0	0
171	O17058240	52	M	0	15	18	17.45	20.86	0	0
172	O17050691	72	M	15.09	13	18	12.23	11.76	0	0
173	O15036382	55	F	0	23	24	17.34	11.23	0	0
174	O17012238	62	F	16.67	20	18	11.56	12.68	0	0
175	O17055115	50	F	0	23	28	14.57	19.43	0	0
176	O17055117	70	F	7.5	13	16	10.43	11.27	0	0
177	O17055113	60	F	7.5	24	23	16.82	13.42	0	0
178	O17055118	65	F	0	19	21	13.78	13.62	0	0
179	O17055108	75	F	15.63	21	27	12.89	15.82	0	0
180	O17055114	70	F	18.75	15	14	10.44	8.45	0	0
181	O08082947	52	M	0	28	30	18.92	20.17	0	0
182	O17055116	65	M	0	23	21	13.22	17.39	0	0
183	O09079502	42	M	0	30	28	17.99	17.32	0	0
184	O17003225	65	F	15.63	18	19	18.43	14.26	0	0
185	O17031915	65	F	9.1	25	25	12.88	16.75	0	0
186	O11049221	57	F	18.18	23	27	14.33	18.62	0	0
187	O17053428	40	F	0	30	30	21.8	19.84	0	0
188	O17021128	31	M	0	30	30	14.8	17.33	0	0
189	O17021136	35	M	2.3	29	25	13.55	20.22	0	0
190	O98023646	65	F	6.8	22	19	10.21	12.81	0	0
191	O17014058	51	M	0	28	19	18.2	18.66	0	0

192	O17013576	51	M	0	19	16	16.25	12.88	0	0
193	O17017782	49	M	0	25	25	15.3	16.44	0	0
194	O12007866	59	M	15.9	30	30	12.78	18.23	0	0
195	O17059033	50	M	0	16	17	15.05	18.54	0	0
196	O17009410	60	M	0	29	30	10.82	9.11	0	0
197	O17008950	65	F	2.8	23	19	12.73	12.06	0	0
198	O17054428	53	M	0	28	30	20.7	19.33	0	0
199	O17069389	59	F	15.63	30	30	12.87	14.84	0	0
200	O17069390	66	M	16.67	24	30	11.34	12.66	0	0

KEY USED IN MASTER DATA

KEY	
Age	
30-40	Group 1
41-50	Group 2
51-60	Group 3
>60	Group 4
Schirmers	
<= 10 mm	1
>10	0
TBUT	
< 6 secs	2
6-10 secs	1
>10 secs	0

OCULAR SURFACE STAINING GRADE	
Absent - Minimal	0
Mild	1
Moderate	2
Marked Severe	3
OSDI Grading	
Normal	0
Mild	1
Moderate	2
Severe	3
Duration of Diabetes	
1-5 years	Cat 1
6-10 years	Cat 2
11-20 years	Cat 3
>20 years	Cat 4
Diabetic Retinopathy Grading	
No DR	0
Mild NPDR	1
Moderate NPDR	2
Severe NPDR	3
PDR	4